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14. ABSTRACT

The objective of this study is to improve our understanding of GWI pathogenesis in two ways through integration across several of the body's regulatory systems of data and knowledge collected from disparate sources, and by mapping of the coordinated interactions between these physiologic systems and the potential for altered "wiring" of these signaling networks in GWI. Using comprehensive molecular profiling, network and control theory the overarching objective of this proposal is to define the precise nature of these irregularities in immune and neuroendocrine signaling as well as the altered activation states of the corresponding cells such that treatment courses can be designed to redirect the system as a whole to normal pattern of coordinated activity.

Active recruitment is under way and seven patients have been consented to participate in the study. Four of the patients are symptomatic with GWI and three are healthy controls. There was a delay in initiating the exercise challenge component of the study due to local requirements, documenting and approvals through several committees on the standard operating procedures for the sterilization of our reusable equipment which consist of a mask attached to the equipment that measures expired gases. This mask is reusable, and has to be cleaned in a particular detergent solution. The VA hospital system recently put into place rigorous standards for documentation of the procedures and adherence to procedures used in sterilizing reusable medical equipment. This protocol's initial subject assessment was delayed while we attempted to expedite this process. The sterilization process was approved by the Infectious Control Committee and the Reusable Medical Equipment committee as of June 23, 2010 and Exercise Challenges will commence the first week of August. Plans are being considered for rapid recruitment by tapping into local TRI county public media attention.

The laboratory measures have been standardized and validated. The analytic plan is being refined, and our co-investigator, Dr Broderick is working with the preliminary data to develop the best method to utilize the data from the preliminary study to validate the findings of the current study. We maintain up to date knowledge of the literature. The PI of this study was tapped to be the Principal Proponent of a large VA cooperative study that hopes to biobank 30,000 GWI era samples, she is very actively engaged in the GWI research and patient advocate community. There is no new literature that would suggest our ongoing study puts research subjects at risk in a newly defined fashion. The study, involving a short exercise challenge and serial blood draws, is a single point in time study, without an intervention.

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Introduction

Within months after their return from Operation Desert Storm an alarming number of Gulf War veterans began to report a variety of symptoms, including fatigue, musculoskeletal discomfort, skin rashes, and cognitive dysfunction. During deployment, these troops were subjected to a number of potentially hazardous conditions and multiple hypotheses as to the etiology of Gulf War Illness (GWI) have been considered. The symptoms of (GWI) that are most consistently reported include those which are often reported in Chronic Fatigue Syndrome (CFS). The objective of this study is to improve our understanding of GWI pathogenesis in two ways; by integration across several of the body's regulatory systems of data and knowledge collected from disparate sources, and by mapping of the coordinated interactions between these physiologic systems and the potential for altered "wiring" of these signaling networks in GWI. Using comprehensive molecular profiling, network and control theory the overarching objective of this proposal is to define the precise nature of these irregularities in immune and neuroendocrine signaling as well as the altered activation states of the corresponding cells such that treatment courses can be designed to redirect the system as a whole to normal pattern of coordinated activity.

Body

The study was approved by the local IRB following the changes that were made recommended by the DOD to meet their requirements. Active recruitment is under way and seven patients have been consented to participate in the study. Four of the patients are symptomatic with GWI and three are healthy controls. There was a delay in initiating the exercise challenge component of the study due to local requirements, documenting and approvals through several committees on the standard operating procedures for the sterilization of our reusable equipment which consist of a mask attached to the equipment that measures expired gases. This mask is reusable, and has to be cleaned in a particular detergent solution. The VA hospital system has recently put into place rigorous standards for documentation of the procedures and adherence to procedures used in sterilizing reusable medical equipment. This protocol's initial subject assessment had been delayed while we attempted to expedite this process. The sterilization process was approved by the Infectious Control Committee and the Reusable Medical Equipment committee as of June 23, 2010. Plans are being considered for rapid recruitment by tapping into local TRI county public media attention.

The laboratory measures have been standardized and validated. The analytic plan is being refined, and our co-investigator, Dr Broderick is working with the preliminary data to develop the best method to utilize the data from the preliminary study to validate the findings of the current study. We maintain up to date knowledge of the literature. The PI of this study was tapped to be the Principal Proponent of a large VA cooperative study that hopes to biobank 30,000 GWI era samples, she is very actively engaged in the GWI research and patient advocate community. There is no new literature that would suggest our ongoing study puts research subjects at risk in a newly defined fashion. The study, involving a short exercise challenge and serial blood draws, is a single point in time study, without an intervention.

Key Research Accomplishments

- Established protocol and completed dry run to work out logistics
- Data Management system was established and tested
- Investigators Meetings took place between Dr. Nancy Klimas, Dr. Mary Ann Fletcher and Dr. Gordon Broderick in Miami, FL in March 2010 and by conference calls every 2 weeks thereafter
- Research Staff was hired and trained in Spring and Summer of 2010
- Received final approval of the revised ICD and Protocol in April 2010
- Internal VA hurdles were cleared after approval was given June 2010 for a Standard of Practice protocol involving the disinfection of the study's Reusable Medical Equipment
- First subjects were recruited June and July 2010
- Initial visits involving the consenting and screening of the recruited subjects were completed
- Exercise Challenge Test scheduled for all screened subjects beginning August 2010
- Next upcoming Investigators meeting is scheduled for September 2010

Reportable Outcomes

We have been using a preliminary data set, supported by a VA Merit, to develop the database and informatics work needed for this work. As the project is in its early stages of recruitment it is premature to list publications emanating from this project. However, the investigators have been developing the analytic platform based on preliminary work and have published 3 papers in the last 6 months based on these analyses. Several more publications are in a rough draft state.

Conclusions

No conclusions up to this point in time.

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Appendices

Appendix A: Journal Publication

Review attached article

"Plasma cytokines in women with chronic fatigue syndrome"

Appendix B: Journal Publication

Review attached article

"Biomarkers in Chronic Fatigue Syndrome: Evaluation of
Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26" R

Appendix C: Journal Publication

Review attached article

"A formal analysis of cytokine networks in Chronic Fatigue Syndrome"
Gordon Broderick, Jim Fuite, Andrea Kreitz, Suzanne D. Vernon, Nancy Klimas, Mary Ann Fletcher
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Appendix D: Journal Publication

Review attached article

"Circadian rhythms in cytokine secretion in Chronic Fatigue Syndrome"
Gordon Broderick, Jim Fuite, Andrea Kreitz, Suzanne D. Vernon, Nancy Klimas, Mary Ann Fletcher
Reply to Editor

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Research

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Plasma cytokines in women with chronic fatigue syndrome

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Abstract

Background: Chronic Fatigue Syndrome (CFS) studies from our laboratory and others have described cytokine abnormalities. Other studies reported no difference between CFS and controls. However, methodologies varied widely and few studies measured more than 4 or 5 cytokines. Multiplex technology permits the determination of cytokines for a large panel of cytokines simultaneously with high sensitivity and with only 30 ul of plasma per sample. No widely accepted laboratory test or marker is available for the diagnosis or prognosis of CFS. This study screened plasma factors to identify circulating biomarkers associated with CFS.

Methods: Cytokines were measured in plasma from female CFS cases and female healthy controls. Multiplex technology provided profiles of 16 plasma factors including the pro -inflammatory cytokines: tumor necrosis factor α (TNFα), lymphotoxin α (LTα), interleukin (IL) - IL-Iα, IL-1β, IL-6; T_H1 cytokines: interferon γ (IFNγ), IL-12p70, IL-2, IL-15; T_H2: IL-4, IL-5; T_H17 cytokines, IL-17 and IL-23; anti-inflammatory cytokines IL-10, IL-13; the inflammatory mediator and neutrophil attracting chemokine IL-8 (CXCL8). Analysis by receiver operating characteristic (ROC) curve assessed the biomarker potential of each cytokine.

Results: The following cytokines were elevated in CFS compared to controls: LTα, IL-1α, IL-1β, IL-4, IL-5, IL-6 and IL-12. The following cytokines were decreased in CFS: IL-8, IL-13 and IL-15. The following cytokines were not different: TNFα, IFNγ, IL-2, IL-10, IL-23 and IL-17. Applying (ROC) curve analyses, areas under the curves (AUC) for IL-5 (0. 84), LTα (0.77), IL-4 (0.77), IL-12 (0.76) indicated good biomarker potential. The AUC of IL-6 (0.73), IL-15 (0.73), IL-8 (0.69), IL-13 (0.68) IL-1α (0.62), IL-1β (0.62) showed fair potential as biomarkers.

Conclusion: Cytokine abnormalities are common in CFS. In this study, 10 of 16 cytokines examined showed good to fair promise as biomarkers. However, the cytokine changes observed are likely to more indicative of immune activation and inflammation, rather than specific for CFS. As such, they are targets for herapeutic strategies. Newer techniques allow evaluation of large panels of cytokines in a cost effective fashion.

Background

According to a Centers for Disease Control (CDC) report [1] the overall prevalence in the USA of Chronic Fatigue Syndrome (CFS), is 235 per 100,000 persons (95% confidence interval, 142-327 per 100,000 persons). Up to 80% of those affected are women [2]. These individuals suffer from severe fatigue that impairs daily activity, diminishes quality of life for years and has no known cure [3]. CFS represents an economic burden for society (e.g., high rates of unemployment due to disability) and healthcare institutions [4]. Hypothetical initiating events for CFS include infections, psychiatric trauma and exposure to toxins. Many of the symptoms are inflammatory in nature (myalgia, arthralgia, sore throat, tender lymphadenopathy), and have prompted a theory of infection induced illness [5,6]. In 60 to 80% of published samples, CFS presents with acute onset of illness, with systemic symptoms similar to influenza infection that do not subside [7]. These observations have led to reports of associated microbial infections or reactivation of latent viral infections [5,8-13]. However, there is no consensus as to etiology.

There is a considerable literature describing immune dysfunction in CFS [14,15]. Elevation of pro-inflammatory cytokines [16,17] and evidence of T_H2 (T helper cell type 2) cytokine activation [15,18] were reported. Other studies reported no difference between CFS and controls. However, methodologies varied widely and few studies measured more than four or five cytokines. Lack of sensitivity of standard ELISA (enzyme-linked immunosorbent assay) technology limited use of plasma for the detection of case/control differences.

Despite evidences of immunological and molecular mediators, no individual marker or combination of markers has been sufficiently associated with CFS to enable its use as a biomarker for the diagnosis or management of CFS. The goal of this study was to determine if, using new technology, plasma cytokines had sufficient sensitivity and specificity to distinguish CFS cases from age-matched healthy controls. Using a multiplex assay, 16 cytokines (T_H1, T_H2, T_H17, pro-inflammatory, anti-inflammatory) were compared among cases and controls. Because of the strong gender bias in CFS (80% female), only women were included in the study.

Methods

Patients

Female CFS patients (n = 40; mean age 50) were from the CFS and Related Disorders Clinic at the University of Miami. A diagnosis of CFS was made using the International Case Definition [19,20]. Female healthy controls (n = 59; mean age 53) were from a NIH funded study. All subjects signed an informed consent approved by the Institutional Review Board of the University of Miami. All CFS study subjects had a SF-36 summary physical score (PCS) below the 50th percentile, based on population norms. Exclusion criteria for CFS included all of those listed in the current Centers for Disease Control (CDC) CFS case definition, including the listed psychiatric exclusions, as clarified in the International CFS Working Group [20]. All CFS subjects were assessed for psychiatric diagnosis at the time of recruitment with the Composite International Diagnostic Instrument [21]. Based on this assessment, we excluded subjects with DSM IV diagnoses for psychotic or melancholic depression, panic attacks, substance dependency, or psychoses as well as any subjects currently suicidal. We also excluded subjects with Borderline or Antisocial Personality Disorder. Subjects had no history of heart disease, COPD, malignancy, or other systemic disorders that would be exclusionary, as clarified by Reeves et al. [20]. Subjects were also excluded for the following reasons: less than 18 yrs of age, active smoking or alcohol history, history of significant inability to keep scheduled clinic appointments in past.

Ethical Issues

This study was approved by the institutional review board and all patients gave written, informed consent.

Blood Collection

Morning blood samples were collected into ethylene diamine tetra acetic acid. Plasma was separated within 2 hours of collection and stored at -80°C until assayed.

Cytokine Array System

We measured 16 cytokines in plasma using Quansys reagents and instrument (Quansys Biosciences, Logan, Utah). The Quansys Imager, driven by an 8.4 megapixel Canon 20D digital SLR camera, supports 96 well plate based chemiluminescent imaging. The Q-Plex™ Human Cytokine - Screen (16-plex) is a quantitative ELISA-based test where sixteen distinct capture antibodies have been absorbed to each well of a 96-well plate in a defined array. Manipulation of the range of the standard curves and exposure time allowed reliable co mparisons between CFS patients and controls of both low and high level cytokine concentrations in plasma. For the standard curves, we used the second order (k = 2) polynomial regression model (parabolic curve), $Y = b_0+b_1X+b_2X^2....+b_kX^k$, where Y caret is the predicted outcome value for the polynomial model with regression coefficients b_1 to k for each degree and y intercept b_0. Quadruplicate determinations were made, i.e., each sample was run in duplicate in two separate assays.

Statistical Analysis

The cytokine measurements were not normally distributed. Since the sample sizes between control and test groups were also different, the nonparametric Kruskal-

Wallis one-way analysis based on rank sums was used to determine the magnitudes of between-group differences. Values of $p < 0.05$ were considered statistically significant. The diagnostic accuracy of those cytokines significantly different among cases and controls was analyzed by receiver operating characteristics (ROC) curve analyses [22] using the Statistical Package for Social Sciences (SPSS) version 16 for Windows.

Results

We clustered the results of the cytokine assays into 5 groups according to the cytokine literature. The results of the individual Kruskal-Wallis analyses are shown in Table 1.

Pro- inflammatory cytokines

A significant elevation in the relative amounts of 4 of 5 pro-inflammatory cytokines in peripheral blood plasma of patients with CFS was found when compared with the controls Only tumor necrosis factor (TNF)α was unchanged. In cases, lymphotoxin (LT)α was elevated by 257% and IL-6 by 100% over the controls.

T_H2 cytokines

Both interleukin (IL)-4 and IL-5 were elevated in CFS, with the median of IL-4 240% and of IL-5 95% higher in cases over controls.

Table 1: Cytokines in Plasma of Female CFS Patients Compared to Female Healthy Controls

CYTOKINE[B]	TYPE	CFS CASES N = 40	CONTROLS N = 59	% DIFFERENCE IN MEDIAN VALUES[C]	KRUSKAL-WALLIS	
					χ^2	P
TNFα	Pro-inflammatory	7.3 (3.4 - 22.6)	6.4 (4.5 - 38.3)	+ 14	0.0	.949
LTα	Pro-inflammatory	7.5 (4.5 - 38.3)	2.1 (4.5 - 12.4)	+ 257	20.4	.000
IL-6	Pro-inflammatory	6.4 (3.8 - 14.4)	3.2 (2.1 - 5.9)	+100	15.1	.000
IL-1α	Pro-inflammatory	3.2 (1.7 - 4.4)	2.3 (0.9 - 3.9)	+ 39	4.1	.044
IL-1β	Pro-inflammatory	13.4 (4.5 - 38.3)	6.2 (4.2 - 38.3)	+ 100	4.2	.041
IFNγ	T_H1	3.1 (0.1 - 11.8)	2.6 (1.2 - 10.6)	+ 19	0.5	.467
IL-2	T_H1	2.3 (1.4 - 5.4)	2.5 (2.1 - 3.5)	- 8	0.6	.420
IL-12	T_H1	4.4 (2.4 - 7.3)	2.0 (1.7 - 2.5)	+ 120	18.8	.000
IL-15	T_H1	13.5 (7.0 - 23.6)	27.4 (19.7 - 49.4)	- 51	15.0	.000
IL-17	T_H17	3.8 (0.8 - 7.2)	2.9 (1.9 - 6.7)	+ 31	0.1	.785
IL-23	T_H17	82.(70.3 - 113)	101.7 (45.0 - 375.6)	- 16	0.8	.814
IL-4	T_H2	1.7 (0.9 - 4.3)	0.5 (.03 - 1.1)	+ 240	20.7	.000
IL-5	T_H2	7.4 (6.3 - 10.0)	3.8 (3.2 - 5.6)	+ 95	33.6	.000
IL-10	Anti-inflammatory	3.3 (2.1 - 5.6)	3.6 (2.2 - 6.4)	- 9	0.1	.748
IL-13	Anti-inflammatory	1.7 (1.2 - 2.1)	2.0 (1.9 - 2.1)	-15	9.6	.002
IL-8 (CXCL8)	NK cell attracting	9. (5.0 - 15.8)	15.4 (11.5 - 22.2)	- 42	9.7	.002

[a] Values are expressed as medians. Values in parentheses are 25th and 75th percentiles.
[b] Cytokines determined as pg/ml.
[c] Percent differences were calculated by using the normal controls as a reference; the + or - sign indicates the direction of change.

Anti-inflammatory cytokines

IL-13 was significantly lower (!5%) in CFS patients while IL-10 was not different.

T_H1 cytokines

Median plasma levels of IL-2 and IFNγ in CFS were similar to those in controls. However, IL-12 was significantly elevated (120%) and IL-15 decreased 15% in cases compared to controls.

IL-8 (CXCL8)

This chemokine was 42% lower in the CFS patients.

T_H17 cytokines

IL-17 and IL-23 were not significantly different in CFS cases compared to controls.

ROC curve analyses

Results for those cytokines that were significantly higher in the case/control comparison are shown in Figure 1 and Table 2. Those for cytokines that were lower in CFS than controls are shown in Figure 2 and Table 3. Area under the curve (AUC) for IL-5 (0. 84), LTα (0.77), IL-4 (0.77), IL-12 (0.76) indicated good biomarker potential. Coordinates of the curves for these 4 cytokines are in Additional File 1. The AUC of IL-6 (0.73), IL-15 (0.73), IL-8 (0.69), IL-13 (0.68) IL-1α (0.62), IL-1β (0.62) showed fair potential as biomarkers (Tables 2 and 3).

Discussion

Several studies report cytokine abnormalities in CFS; however, the findings are mixed. Differences between reports may be largely due to differences in methodologies [14]. Amounts of cytokines in plasma or serum are often below the level of detection in traditional ELISA assays. In addition to assay sensitivity, results using the direct approach are influenced by length of time following blood draw to separation of serum or plasma, temperature of storage and repeated thawing and freezing. *In vitro* stimulation whole blood or peripheral blood mononuclear cells (PBMC) is another approach to study cytokines. ELISA is then used to measure cytokine content of supernatants of culture fluids. Obviously, results depend on culture conditions and stimulants used. Other techniques include either in unstimulated or stimulated PBMC. Results obtained with these methodologies are not directly comparable.

The availability of sensitive multiplex technology permitted the determination of 16 cytokines simultaneously on plasma samples from female CFS patients and age and gender matched healthy controls. In the CFS cases, we found an unusual pattern of the cytokines that define the CD4 T cell. Dendritic cell derived IL-12, the main T_H1-inducing cytokine leading to production of IFNγ, IL-2 and TNFα, was elevated. However, IFNγ, IL-2 and TNFα were unchanged in plasma of CFS cases compared to controls. Another dendritic cell derived cytokine, IL-15, was decreased. IL-2 and IL-15 are key participants in CD8 T cell and NK cell activation and function. Sharing the beta and gamma receptor subunits results in several common functions: e.g. cytotoxicity. On the other hand, due to their distinct alpha receptor subunits, they play opposing roles in immune processes such as activation induced cell death (IL-2) and immunological memory (IL-15) [23]. IL-23 (unchanged between controls and cases) stimulates the differentiation and function of the T_H17 subset of CD4 T cells, a relatively newly described immune defense. The T_H17 CD4 cell produces IL-17, protects surfaces (e.g., skin, lining of the intestine) against bacteria, and plays a critical role in chronic intestinal inflammation [24,25]. The unchanged IL-17 and IL-23 levels in CFS noted in this study would argue against bacterial gastrointestinal infections as playing an important role in persistent illness.

Along with the T_H1 abnormalities, we found up regulation of T_H2 associated cytokines, IL-4 and IL-5, in the CFS subjects. Allergy is common in CFS cases. Years ago, Straus et al, reported >50% atopy in 24 CFS patients [26]. The elevation of these two cytokines implies a type 2 shift - and diminished stimulus for cytotoxic lymphocyte function.

Table 2: AUC for Plasma Cytokines Significantly Higher in CFS Cases vs. Controls

Cytokines	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Boundary	Upper Boundary
LTα	.769	.049	.000	.673	.865
IL-6	.731	.050	.000	.633	.828
IL-1α	.620	.056	.044	.509	.730
IL-1 β	.621	.062	.041	.499	.744
IL-5	.844	.041	.000	.764	.925
IL-4	.770	.048	.000	.676	.864
IL-12	.758	.054	.000	.653	.863

[a] Under the nonparametric assumption
[b] Null hypothesis: true area = 0.5

Table 3: AUC for Plasma Cytokines Significantly Lower in CFS Cases vs. Controls

Cytokines	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Boundary	Upper Boundary
IL-8	.685	.062	.002	.564	.806
IL-15	.731	.056	.000	.620	.841
IL-13	.682	.064	.002	.556	.808

[a] Under the nonparametric assumption
[b] Null hypothesis: true area = 0.5

The probability of chronic inflammation [17] in CFS is supported by the elevation of four members of the pro-inflammatory cytokine cascade [27], LTα, IL-1α, IL-1β, and IL-6, in the CFS samples compared to controls. The exception was TNFα, although the median value for cases was 14% higher than controls and about 1/4 of CFS patients in other studies had elevated TNFα [15,17]. Interleukin-13, associated with inhibitory effects on inflammatory cytokine production, was lower in cases compared to controls. The anti-inflammatory cytokine, IL10, was not different. The inflammatory mediator IL-8 (a chemokine known as CXCL8) known to be responsible for the migration and activation of neutrophils and NK cells [28] was decreased in plasma of CFS patients.

The observations of abnormal cytokine patterns in CFS patients support the reports of retrovirus infections and reactivation of latent herpes virus infections. DeFreitas, et al found HTLV-II- like gag sequences by polymerase chain reaction and in situ hybridization as well as antibodies reactive with human T- lymphotropic virus (HTLV) in a majority of 30 CFS cases. Twenty healthy controls were negative for the three assays [11]. Holmes, et al, reported that structures consistent with stages of a Lentivirus replicative cycle were observed by electron microscopy in 12-day PBMC cultures from 10 of 17 CFS patients and not in controls [12]. Recently, DNA from a human gammaretrovirus, xenotropic murine leukemia virus-related virus (XMRV), was found in the PBMC of 68 of 101 patients compared to 8 of 218 healthy controls. Patient-derived, activated PBMC produced infectious XMRV *in vitro*. Both cell associated and cell-free transmission of the virus to

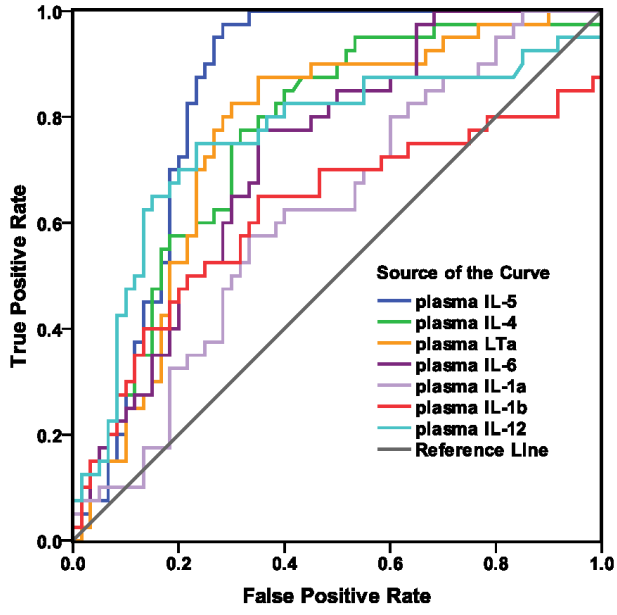

Figure 1
ROC curves shows the classification performance of plasma cytokines from CFS cases and healthy controls. Curves are for the 7 cytokines significantly elevated ($p < .05$) in cases compared to controls (IL-4, IL-5, IL-12, LTα, IL-1α, IL-1β, and IL-6).

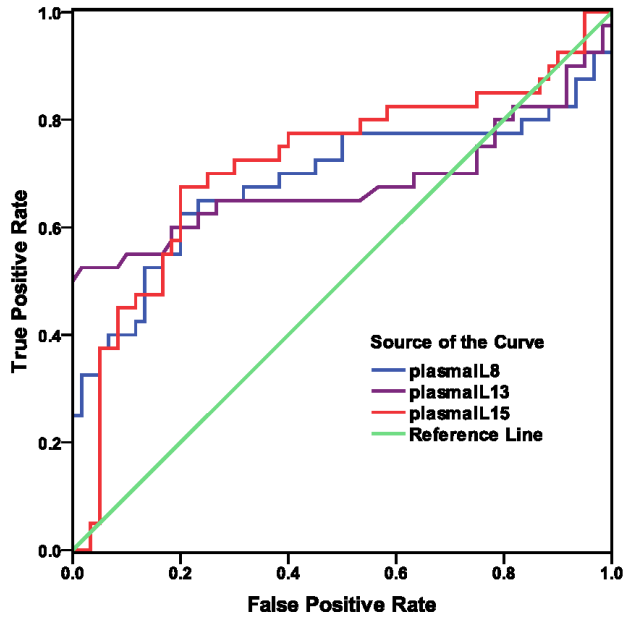

Figure 2
ROC curves show the classification performance of plasma cytokines from CFS cases and healthy controls. Curves are for the 3 cytokines significantly lower ($p < .05$) in cases compared to controls (IL-8, IL-13 and IL-15).

uninfected primary lymphocytes and indicator cell lines was possible [13]. The XMRV *gag* and *env* sequences discovered in CFS cases were more than 99% similar to those previously reported for prostate tumor-associated strains of XMRV [29].

Latent herpes virus infections are likely to be important in CFS. Immunologic effects of persistent herpetic infections do not require of virus DNA synthesis. For example, Glazer and colleagues [9] reported that EBV encoded deoxyuridine triphosphate nucleotidohydrolase (dUTPase) upregulated the production of proinflammatory cytokines, including IL-1β and IL-6. Also, dUTPase administered to mice, produced sickness behaviors known to be induced by some of the cytokines we showed to be upregulated. A subsequent paper showed that EBV-encoded dUTPase can enhance production of proinflammatory cytokines by monocytes/macrophages in contact with endothelial cells of blood vessels [30]. In addition, Ariza, et al demonstrated that the purified EBV-encoded dUTPase activated NFkappaB in a dose-dependent through Toll Like Receptor 2 (TLR2). Treatment of human monocyte-derived macrophages with an anti-EBV-encoded dUTPase or with an anti-TLR2 blocked the production of IL-6 [31]. Iwakiri, et al reported that EBV-encoded small RNA (EBER), which is released from EBV-infected cells, was responsible for immune activation by EBV, including release of proinflammatory cytokines [32]. A recent study (M Vera, MA Fletcher, C Cuba, L Garcia, N Klimas, presented to the International Association for Chronic Fatigue Syndrome/Myalgic Encephalitis, Reno, NV, March, 2009) reported that the anti-viral and immuno-modulatory drug, inosine pranobex, led to significant improvement in the clinical scores of 61 patients treated for 6 months. Immune activation was decreased, NK cell activity was improved and titers of anti-Epstein Barr Virus Viral Capsid Antigen IgG were significant decreased. Antibody titers to Human Herpes Virus 6 were unchanged. A larger randomized trial would seem appropriate.

According to ROC analysis, plasma IL-5 was best at distinguishing CFS cases from controls, with the highest percentage difference from the median of normal and the largest AUC. We recently reported elevation of IL-5 in the supernatants of mitogen-stimulated cultured lymphocytes from Gulf War Illness (GWI) cases compared to controls [33]. The symptoms of GWI are similar to those reported in CFS. Three other cytokines with AUC values consistent with good potential as biomarkers were LTα, IL-4 and IL-12. Less promising as systemic markers of CFS, but with AUC significantly different in cases compared to controls, were IL-6, IL-15, IL-13, IL-1α and IL-1β.

The cytokine changes observed between CFS patients and healthy, matched controls are likely to be indicative of immune activation and inflammation. Fibromyalgia, GWI, rheumatologic disorders and multiple sclerosis may have similar cytokine patterns. Future research will be required to determine if the cytokine patterns associated with CFS cases are similar or distinct from other complex, chronic and poorly understood illnesses.

Obvious limitations of this study are that the samples represent a single point in time and a single gender. The parent protocol, from which the CFS samples were gathered, is a larger longitudinal study. Subjects are followed over 18 months and sample collection includes times of relative symptom remission or exacerbation. Completion of the study will allow the correlation of CFS related symptoms and other immune markers with the cytokine patterns. CFS is a condition that affects women in disproportionate numbers. The larger study will have sufficient power to allow the study of cytokine patterns in men with CFS. As Broderick and colleagues have pointed out, markers of immune status tend to be highly variable and context-specific leading to inconsistent biomarker lists [34]. These indicators are parts of a complex and integrated system and their inter-dependency must be addressed. Accordingly, we are currently engaged in combining the proteomic and genomic data on cytokines with other immunologic and neuroendocrine markers, both proteomic and genomic, in order to map the network structure of neuroendocrine-immune interaction in CFS. We will focus on identifying associations between nodes that are differentially expressed across disease group and controls.

The finding of cytokine imbalances in the peripheral blood compartment has implications for physiological and psychological function changes. The decreased natural killer (NK) cell cytotoxic and lymphoproliferative activities and increased allergic and autoimmune manifestations in CFS would be compatible with the hypothesis that the immune system of affected individuals is biased towards a T- helper (T_H) 2 type, or humoral immunity-oriented cytokine pattern. The elevations in LTα, IL-1α, IL1β and IL-6 indicate inflammation, likely to be accompanied by autoantibody production, inappropriate fatigue, myalgia and arthralgia, as well as changes in mood and sleep patterns.

Conclusion

This is study is among the first in the CFS literature to report the plasma profiles of a reasonably large panel of cytokines assessed simultaneously by multiplex technique. Cytokine abnormalities appear to be common in CFS. Several showed promise as potential biomarkers. The changes from the normal condition indicate immune acti-

vation and inflammation - and point to potential therapeutic strategies. The results imply a disorganized regulatory pattern of T_H1 function, critical to antiviral defense. The data from this study support a T_H2 shift, pro-inflammatory cytokine up regulation and down regulation of important mediators of cytotoxic cell function.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MAF and NGK conceived of the study, participated in its design, coordination, performed the statistical analysis and drafted the manuscript; NGK and SL participated in patients' diagnosis and assessment; ZB participated in subject recruitment and data management; XRZ carried out the immunoassays. All authors read and approved the final manuscript.

Additional material

Additional file 1

Coordinates of the curves for those cytokines with AUC that indicated good biomarker material.

Click here for file

[http://www.biomedcentral.com/content/supplementary/1479-5876-7-96-S1.doc]

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Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26

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Abstract

Background: Chronic Fatigue Syndrome (CFS) studies from our laboratory and others described decreased natural killer cell cytotoxicity (NKCC) and elevated proportion of lymphocytes expressing the activation marker, dipeptidyl peptidase IV (DPPIV) also known as CD26. However, neither these assays nor other laboratory tests are widely accepted for the diagnosis or prognosis of CFS. This study sought to determine if NKCC or DPPIV/CD26 have diagnostic accuracy for CFS.

Methods/Results: Subjects included female and male CFS cases and healthy controls. NK cell function was measured with a bioassay, using K562 cells and ^{51}Cr release. Lymphocyte associated DPPIV/CD26 was assayed by qualitative and quantitative flow cytometry. Serum DPPIV/CD26 was measured by ELISA. Analysis by receiver operating characteristic (ROC) curve assessed biomarker potential. Cytotoxic function of NK cells for 176 CFS subjects was significantly lower than in the 230 controls. According to ROC analysis, NKCC was a good predictor of CFS status. There was no significant difference in NK cell counts between cases and controls. Percent CD2+ lymphocytes (T cells and NK cells) positive for DPPIV/C26 was elevated in CFS cases, but there was a decrease in the number of molecules (rMol) of DPPIV/C26 expressed on T cells and NK cells and a decrease in the soluble form of the enzyme in serum. Analyses by ROC curves indicated that all three measurements of DPPIV/CD26 demonstrated potential as biomarkers for CFS. None of the DPPIV/C26 assays were significantly correlated with NKCC.

Conclusions: By ROC analysis, NKCC and three methods of measuring DPPIV/C26 examined in this study had potential as biomarkers for CFS. Of these, NKCC, %CD2+CD26+ lymphocytes and rMol CD26/CD2+ lymphocyte, required flow cytometry, fresh blood and access to a high complexity laboratory. Soluble DPPIV/C26 in serum is done with a standard ELISA assay, or with other soluble factors in a multiplex type of ELISA. Dipeptidyl peptidase IV on lymphocytes or in serum was not predictive of NKCC suggesting that these should be considered as non-redundant biomarkers. Abnormalities in DPPIV/CD26 and in NK cell function have particular relevance to the possible role of infection in the initiation and/or the persistence of CFS.

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Introduction

Chronic Fatigue Syndrome (CFS) is characterized by persistent and unexplained fatigue resulting in severe impairment in daily function and is defined by symptoms, disability, and exclusion of medical and psychiatric conditions that could explain the fatigue [1,2]. Population-based studies estimated the prevalence of CFS at 0.23% to 0.41% [3,4]. Costs to the US economy were estimated at $9 billion in lost productivity and up to $24 billion dollars in health care expenditures annually [5–7]. Complications and co-morbidity can be severe. For example, CFS was associated with chronic or episodic cardiovascular and autonomic dysfunction [8]. Recent results from our group demonstrated reduced stroke volume and cardiac output in more severely afflicted CFS patients [9]. Reports suggested increased risk of cancer as well as suicide [10,11]. CFS affects all ethnic groups and socio-economic strata of society though at least 2 to 4 times as many women as men suffer from this illness [3,12,13]. Diagnosis using the case definition [1] requires the exclusion of any other medical explanation for these symptoms, yielding an inefficient, slow, error prone process. This is also costly because current clinical diagnosis typically involves tertiary care specialists.

Like many chronic illnesses CFS pathophysiology is complex and affects several of the body's main regulatory systems. There is a considerable literature describing immune dysfunction in CFS [14–16], although reviews of the immunology of CFS noted that universal agreement of immunological abnormalities had not been achieved, in no small part due to differences in methodologies, case definition and study quality [17,18]. However, redundant reports support 1) reduced function of natural killer (NK) cells [14,19] with deficiencies of perforin and granzymes in both NK cells and CD8 T cells [20]; 2) inflammation [21,22]; 3) altered cytokine profiles [9,10] with elevation of proinflammatory cytokines [11,12] and Th2 (T helper cell type 2) polarization [11,13]; and 4) chronic lymphocyte activation [14,16].

Current research efforts are directed toward identifying an individual marker or combination of markers sufficiently associated with CFS to facilitate objective diagnosis and management of CFS. Previously we reported that CFS patients with poor NK function had more fatigue, less vigor, more daytime dysfunction, and more cognitive impairment. Those results provided preliminary evidence in support of using NKCC as subgroup marker for disease severity in CFS [23].

Present on the surface of many cells including lymphocytes, DPPIV/CD26 is a transmembrane glycoprotein and a serine peptidase that spits proline dipeptides from the N-terminus of polypeptides, including chemokines and neuropeptides. An enzymatically active soluble form is found in serum. We have observed an elevated proportion of lymphocytes expressing this activation marker in CFS patients as compared to controls [14].

No widely accepted laboratory tests are available for the diagnosis or prognosis of CFS. This study sought to determine the accuracy by which measurements of NKCC or DPPIV/CD26 distinguished between subjects with the clinically derived diagnosis of CFS and matched healthy controls.

Methods

Objectives

Prior work indicated defective NK cell function and a high percent of T cells and NK cells expressing the activation marker DPPIV/CD26 in CFS cases. The aim of this study was to determine the potential of NKCC and DPPIV/CD26 as biomarkers for CFS.

Participants

Chronic fatigue syndrome patients (age 18 to 60, mean age 44; 83% female) were drawn from the University of Miami Miller School of Medicine CFS and Immunodeficiency Clinic after they were diagnosed with CFS using the CDC clinical diagnostic criteria [1,2] (Table 1). All were participants in research studies (NIH, Chronic Fatigue and Immunodeficiency Syndrome Association (CFIDS) or University of Miami). Exclusion criteria included any active medical condition that could explain the presence of chronic fatigue, including diabetes, the current use of immunomodulatory or antibiotic medications, and a past or present psychiatric diagnosis of psychosis (e.g., schizophrenia), dementia, major depressive disorder with psychotic or melancholic features, bipolar disorder, anorexia or bulimia nervosa, or alcohol/substance abuse within two years of the onset of the fatigue or anytime thereafter. The CFS subjects were studied at 2 to 25 years after onset of symptoms, with an average onset of 10 years. Healthy controls (Table 1) (age 23–74, mean age 41, 86% female) were drawn from University of Miami, NIH or CFIDS funded studies. Each completed a medical and psychiatric history that included medications and alcohol/substance abuse. Those with active medical or psychiatric conditions, immunomodulating medications or alcohol/substance abuse were excluded.

Description of Procedures or Investigations Undertaken

Blood Collection. Morning blood samples were collected. For lymphocyte function assays and flow cytometry, sodium heparin tubes were used. The samples were held at room temperature and delivered to the laboratory within 4 hours. For complete blood counts, the blood was collected into ethylene diamine tetra acetic acid and delivered to the laboratory within 4 hours. Serum was separated from blood clot within 4 hours of collection into red stopper tube and stored at $-20^{\circ}C$ until assayed.

Natural killer cell cytotoxicity. The bioassay for NKCC was performed using whole blood within 8 hours of collection in a chromium release assay as previously described [24]. The NK sensitive erythroleukemic K562 cell line was used as the target cell. The assay was done in triplicate at four target-to-effector cell ratios with 4-hour incubation. The % cytotoxicity at each target-to-effector ratio and number of CD3-CD56+ (NK) cells per unit of blood was used to express the results as % cytotoxicity at a target-to-effector cell ratio of 1:1.

Determination of Lymphocyte Subsets and Assessment of Cell Surface Protein Concentrations by Quantitative Fluorescence. For the assessment of lymphocyte subsets, and the quantitative fluorescence intensity studies of cell surface antigen, a whole blood lysis method was used [25]. Whole blood samples were stained in 4 color combinations, with optimized (saturating) concentrations of antibodies, erythrocytes were lysed and the cell fixed with the Optilyse C reagent (Beckman-Coulter Corp., Hialeah, FL). Determination of lymphocyte, monocyte and granulocyte populations was determined using light scatter and back gating on fluorescence for the CD45 bright and CD14

Table 1. Natural killer cell cytotoxicity and dipeptidyl peptidase IV/CD26 in chronic fatigue syndrome cases[a] compared to controls[b].

Variable	*Number of CFS Cases*	*Median (25–75th percentile)*	*Number of Healthy Controls*	*Median (25–75th percentile)*	*p*
NKCC%	176	12 (8–21)	230	28 (20–37)	.000
% CD26+CD2+ Cells	75	61 (55–66)	100	52 (47–59)	.000
sCD26 in Serum (ng/ml)	73	489 (396–643)	122	671 (496–871)	.000
rMol CD26/CD2+ Cell	77	3625 (2844–4633)	102	4388 (3600–5388)	.001

[a]>80% female, average age 48;
[b]>80% female, average age 47.
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negative population using a Beckman Coulter multiparameter flow cytometer. The isotype control was the reference for negative events. Spectral compensation was established daily. Quality control included optimization for lymphocyte recovery, purity of gate of analysis, lymphosum, and replicate determinations. Phycoerythrin (PE) labeled antibodies were used for quantitative fluorescence determinations and the median fluorescence intensity value was entered into a least squares linear regression equation derived from analysis of the QuantiBrite fluorescence intensity standards (Beckton Dickenson, San Jose, CA). This permitted conversion from fluorescence intensity values to median numbers of molecules PE bound per cell (relative numbers of molecules protein expressed per cell at saturating concentrations of antibody; rMol/cell). This technique allowed us to determine the relative (r) number of molecules (Mol) of CD26 on CD2+ lymphocytes (T cells and NK cells) (Figure S1).

Assay of Soluble CD26. Soluble CD26 in serum was assayed with an ELISA kit from Bender MedSystems (Vienna, Austria). This assay has a sensitivity of 7.26 ng/ml and precision of 4.6%.

Ethical issues. All subjects signed an informed consent approved by the University of Miami Institutional Review Board. Participants were English speaking with at least an 8th grade education to ensure they were able to comprehend the informed consent as well as read and complete the questionnaires.

Statistical Methods. The nonparametric Mann-Whitney test was used to determine the magnitudes of between-group differences. The nonparametric Spearman test was used to determine correlations. Values of $p<0.05$ were considered statistically significant. The diagnostic accuracy of biomarkers was assessed in terms of true positive (sensitivity) versus true negative (1-specificity) using nonparametric receiver operating characteristics (ROC) analyses [26] available in the Statistical Package for Social Sciences (SPSS) software for Windows (SPSS Inc, Chicago, IL). The nonparametric ROC plot uses all of the data, makes no parametric assumptions and provides unbiased estimates of sensitivity and specificity, indicating the ability of a test to discriminate between two alternate states of health, in this case, CFS cases and healthy controls. The calculation of the area under the curve (AUC) provides a convenient single number. An AUC>0.5 indicates that the test shows no difference between the two groups while AUC = 1.0 is found if the test gives a perfect separation between groups. The coordinates of the curves (COC), which provide the entire spectrum of sensitivity/specificity pairs and a complete picture of test accuracy, are given in Supplementary Files for each ROC plot.

Results

Natural killer cell cytotoxicity

The NKCC values were significantly lower in cases than controls ($p<.000$) (Table 1). Numbers of NK cells were not different between CFS and controls. The values for CD3-CD56+ lymphocytes/cumm (expressed as median (25th–75th percentile) were: 176 (134–256) for CFS and 236 (151–336) for controls. According to the nonparametric ROC curve for 406 samples, as shown in Figure 1, NKCC was a good predictor of CFS status. Smaller values for NKCC indicated evidence for a positive actual state (CFS).The area under the curve (AOC) is shown in Table 2. The coordinates of the curve (COC) are given in Table S1.

Dipeptidyl peptidase IV/CD26

We measured this peptidase on cell surfaces and in serum in a subset of samples for which we had assayed NKCC. The results shown in Table 1, with CFS compared to controls, indicated an elevation of the percent of CD26+ CD2+ lymphocytes, but a decrease in the number of molecules of CD26 on T cells and NK cells and a decrease in the soluble form of CD26 in serum. ROC curve analyses and AUC, shown in Table 2 and Figures 2, 3, and 4 indicated that all three measures of CD26 have potential as biomarkers for CFS (see COCs in Tables S2, S3, and S4). The qualitative flow cytometry assay for proportion of CD26+CD2+ lymphocytes and the ELISA assay of sCD26 in serum were good predictors. The quantitative flow method for concentration of CD26 on CD2+ lymphocytes was less precise. Spearman analyses showed that none of the CD26 assays were significantly correlated with NKCC (data not shown).

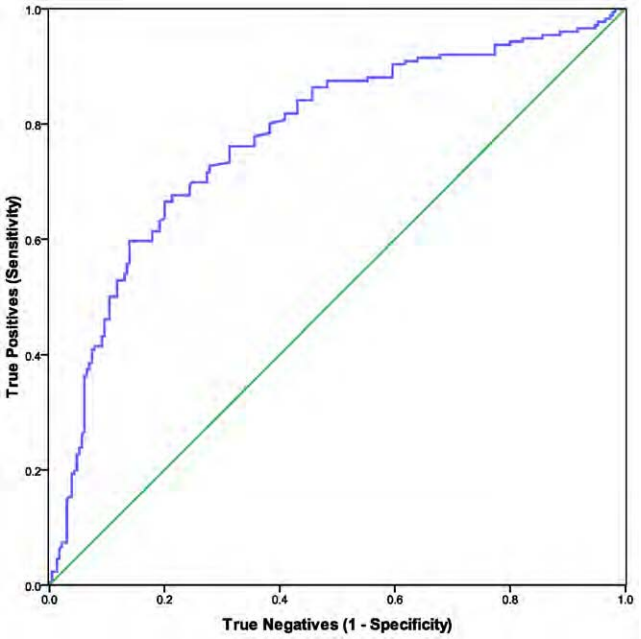

Figure 1. ROC analyses were used to evaluate NKCC as a predictor of CFS. The nonparametric ROC plot (blue curve) indicated the ability of NKCC to discriminate between CFS cases and healthy controls. Smaller values for NKCC were associated with CFS cases. The 45 degree line (green) indicates the theoretical plot of a test with no discrimination between CFS and controls.
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Discussion

Data from this and earlier studies gave credible support to diminished NKCC function in CFS. These effector cells of the innate immune system have an important role in antiviral, antibacterial, and antitumor immunity, but were deficient as measured by direct cytolysis of target cells, and as determined by measurement of intra cellular lytic proteins [14,20]. In 60 to 80% of published samples, CFS presented with acute onset of illness, with systemic symptoms similar to influenza infection that did not subside [14]. The sudden onset, the symptoms of myalgia, arthralgia, sore throat and tender lymphadenopathy prompted a theory of infection induced illness [14,27]. Published reports both support and deny associated microbial infections, reactivation of latent herpes virus infections and/or retrovirus infections in CFS [28–35]. Of interest is the finding by Glaser and colleagues that the adverse immunologic effects of persistent infections with Epstein Barr Virus (EBV) did not require viral DNA synthesis [36]. Some published work suggested the possibility of elevated risk for cancer in patients with CFS [10–11], though to date there

Table 2. ROC curve analysis: Area Under the Curve (AUC) for natural killer cell cytotoxicity and dipeptidyl peptidase IV/CD26 in chronic fatigue syndrome cases compared to controls.

Variables	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NKCC%	.776	.024	.000	.729	.823
CD2+CD26+%	.746	.037	.000	.674	.818
sCD26 ng/ml	.732	.036	.000	.652	.794
rMolCD26/CD2+ cell	.650	.042	.001	.568	.733

[a]Under the nonparametric assumption;
[b]Null hypothesis: true area = 0.5.
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has been no long term natural history study to accurately assess this risk.

Previously, we showed that the proportion of lymphocytes (NK cells and T cells) expressing CD26 is elevated in CFS cases [14]. In the present study, we found the density of DPPIV/CD26 on lymphocyte surfaces and the concentration of the enzyme in plasma is reduced in CFS subjects, compared to controls. We hypothesize that this reduction is due to chronic lymphocyte activation in CFS patients. The present study adds to the evidence of loss of innate immune function and chronic immune activation, resulting from the long term presence of antigenic stimulus, either self or foreign. Compared to healthy controls, chronic hepatitis C patients had significantly lower serum soluble CD26 levels [37]. In another study, acute, self-limiting infection with live influenza vaccine and chronic infection with persistent antigen, such as with cytomegalovirus (CMV), EBV or human immunodeficiency virus (HIV), was compared using multi-parameter flow cytometry and tetramer technology. These analyses identified a unique pattern of high density DPPIV/CD26 expression among influenza-specific CD8 T cells, but not among CD8 T cells specific for CMV, EBV (three different epitopes) or HIV [38]. These findings were interpreted as indicating that expression of CD26 (high) is characteristic of a memory cell, present in acute infection but not in chronic infection.

Dipeptidyl peptidase IV/CD26 cleaves N-terminal X-Pro dipeptides from peptides. The peptidase controls the *in vivo* half-life of the proinflammatory chemokine stromal cell-derived factor-1 (SDF-1). Mice deficient in DPPIV/CD26 exhibited increased levels of circulating active SDF-1, associated with increased numbers of SDF-1 receptor (CXCR4)-positive cells infiltrating

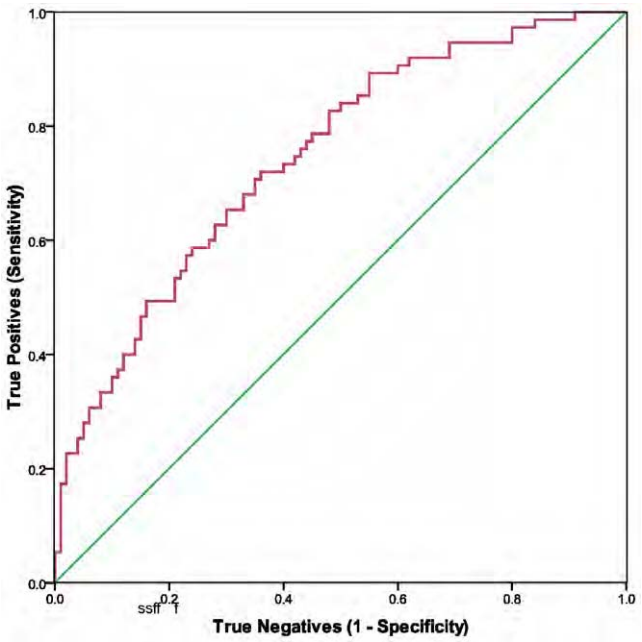

Figure 2. ROC analyses were used to evaluate %CD26+CD2+ lymphocytes as a predictor of CFS. The nonparametric ROC plot (purple curve) indicated the ability of %CD26+CD2+ lymphocytes to discriminate between CFS cases and healthy controls. Larger values for %CD26+CD2+ lymphocytes were associated with CFS cases. The 45 degree line (green) indicates the theoretical plot of a test with no discrimination between CFS and controls.
doi:10.1371/journal.pone.0010817.g002

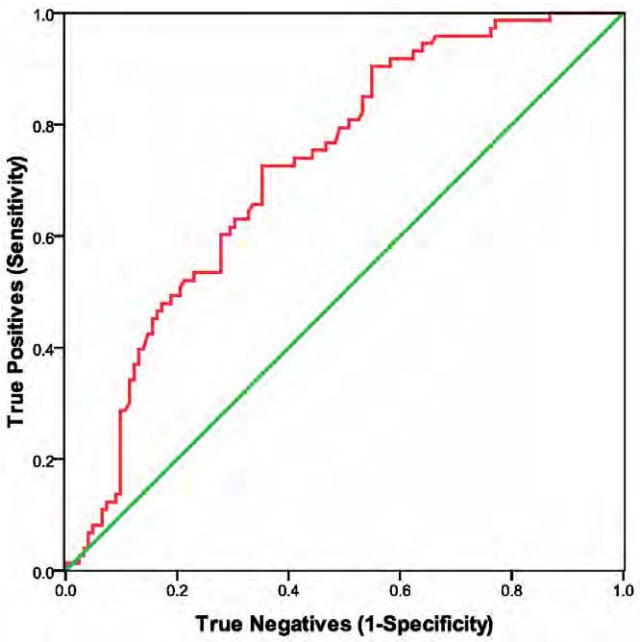

Figure 3. ROC analyses were used to evaluate serum dipeptidyl peptidase IV/CD26 as a predictor of CFS. The nonparametric ROC plot (red curve) indicated the ability of serum dipeptidyl peptidase IV/CD26 to discriminate between CFS cases and healthy controls. Smaller values were associated with CFS cases. The 45 degree line (green) indicates the theoretical plot of a test with no discrimination between CFS and controls.
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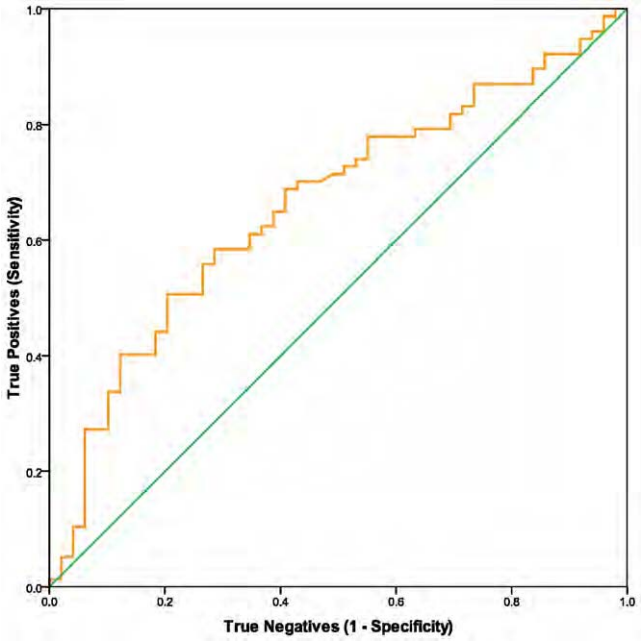

Figure 4. ROC analyses were used to evaluate relative number of molecules of dipeptidyl peptidase IV/CD26 on the surface of CD2+ lymphocytes as a predictor of CFS. The nonparametric ROC plot (orange curve) indicated the ability of number of molecules of dipeptidyl peptidase IV/CD26 on the surface of CD2+ lymphocytes to discriminate between CFS cases and healthy controls. Smaller values were associated with CFS cases. The 45 degree line (green) indicates the theoretical plot of a test with no discrimination between CFS and controls. cell at saturating concentrations of antibody; rMol/cell) is shown.
doi:10.1371/journal.pone.0010817.g004

arthritic joints [39]. In a clinical study, by the same researchers, plasma levels of DPPIV/CD26 from rheumatoid arthritis patients were significantly decreased when compared to those from osteoarthritis patients and inversely correlated with C-reactive protein levels. They postulated that decreased circulating soluble DPPIV/CD26 levels in arthritis may influence DPPIV/CD26-mediated regulation of the chemotactic SDF-1/CXCR4 axis. These patients have elevated number of T cells expressing DPPIV/CD26 and reduced DPPIV enzymatic activity and DPPIV/CD26 antigen in plasma compared to controls [39,40].

Dipeptidyl peptidase IV/CD26 causes the degradation of glucagon-like peptide 1 (GLP-1), an incretin hormone [41]. Inhibitors of DPPIV/CD26 such as sitagliptin, which prevent the degradation of GLP-1 [42], are now marketed for the treatment of type 2 diabetes mellitus (T2DM). Considering that DPPIV/CD26 has a key role in immune regulation as a T cell activation molecule and in immune-mediated disorders, it is noteworthy that the effects of inhibition of DPPIV/CD26 on the immune system have not been extensively investigated. There are reports that infections were increased after sitagliptin treatment [43]. So far, only routine laboratory safety variables have been measured in published randomized controlled trials.

Administration of DPPIV/C26 inhibitors for the treatment of T2DM patients could influence immune function, including NKCC. A study of CD26 gene knockout mice concluded that DPPIV/C26 contributes to the regulation of development, maturation and migration of CD4 T, NK and NKT cells, cytokine secretion, T cell-dependent antibody production and immunoglobulin isotype switching of B cells [44]. An initial diagnosis of CFS would not be made in the patient with obvious T2DM. However, the frequency of development of T2DM after diagnosis of CFS is not known–nor is the effects of a DPPIV/C26 inhibitor in the CFS patient.

Duration of illness typically exceeds 10 years. Persistence may involve complex interaction of immune, autonomic and neuroendocrine regulation and remains poorly understood. It is important to recall that the associated chronic inflammation can have important consequences on energy metabolism by promoting insulin resistance [45]. This chronic inflammatory state would also support a concurrent low-grade Th1 response by inhibiting the protective effects of T regulatory cell subset via increased IL-6 expression. The decreased NKCC and the abnormal DPPIV/C26 manifestations in CFS would be compatible with the hypothesis that the immune system of affected individuals is biased towards a T- helper (Th) 2 type, or humoral immunity-oriented cytokine pattern.

The data obtained on NK cell function, immune activation and DPPIV/C26 on cell surfaces and in serum, are consistent with a viral etiology for CFS. The elevated proportion of activated CD4 and CD8 T cells and defective NKCC in CFS cases suggests that T cells are metabolically limited in performing their helper function. The abnormalities observed may have applications with other complex, chronic and poorly understood illnesses, including fibromyalgia, gulf war illness, rheumatologic disorders and multiple sclerosis—though the precise constellation of patterns observed with these biomarkers may differ in each. However, the specific panel that we have identified here are likely to be helpful as objective markers for diagnosing CFS, determining subgroups, following patients over time and as targets for therapeutic strategies. These indicators are parts of a complex and integrated system and their inter-dependency must be addressed [46]. Accordingly, we are currently engaged in mapping the network structure of neuroendocrine-immune interaction in CFS

Limitations

Obvious limitations of this study are that each patient sample represents a single point in time. To address this, we are conducting a large longitudinal study to follow 150 subjects over 18 months. Samples are collected during times of relative symptom remission and exacerbation. Completion of the study will allow the correlation of CFS related symptoms with lymphocyte function and activation. Because CFS is a condition that affects women in disproportionate numbers, over eighty percent of the cases in the present study were female. The larger study will have sufficient power to allow a sub study of biomarker patterns in men with CFS.

Conclusions

The predominance of evidence indicating that people with CFS have decreased function of NK cells and abnormal activation of T and NK cells was supported by this study. The purpose of the study was to determine usefulness of these measurements as biomarkers. By ROC analysis, NKCC and dipeptidyl peptidase/CD26 were identified as potential biomarkers for CFS through their demonstrated accuracy in discriminating CFS patients from healthy controls. Dipeptidyl peptidase/CD26 on lymphocytes or in serum was not correlated with NKCC, suggesting that these are non-redundant biomarkers. Current CFS treatments are directed at reducing symptom severity but no cure exists for this condition. The findings of this study give support to the concept that cause and/or the pathophysiology of CFS are related to infection. These findings may lead to therapeutic approaches. The specter of

infectious disease further emphasizes the significance of this research to public health.

Supporting Information

Figure S1 Illustration of technique used to convert fluorescence intensity values to median numbers of molecules PE bound per cell (relative numbers of molecules protein expressed per cell at saturating concentrations of antibody; rMol/cell).
Found at: doi:10.1371/journal.pone.0010817.s001 (0.38 MB TIF)

Table S1 Coordinates of the Curve for NKCC.
Found at: doi:10.1371/journal.pone.0010817.s002 (0.23 MB DOC)

Table S2 Coordinates of the ROC Curve for CD26+CD2+ Lymphocytes in CFS Compared to Controls.
Found at: doi:10.1371/journal.pone.0010817.s003 (0.20 MB DOC)

Table S3 Coordinates of the ROC curve for sCD26.
Found at: doi:10.1371/journal.pone.0010817.s004 (0.17 MB DOC)

Table S4 Coordinates of the curve for rMolCD26CD2+.
Found at: doi:10.1371/journal.pone.0010817.s005 (0.28 MB DOC)

Author Contributions

Conceived and designed the experiments: MAAF KM NGK. Performed the experiments: XRZ KM. Analyzed the data: MAAF GJB. Contributed reagents/materials/analysis tools: SL BH MA. Wrote the paper: MAAF NGK. Critically reviewed paper: BH, MA, GJB.

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A formal analysis of cytokine networks in Chronic Fatigue Syndrome

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ABSTRACT

Chronic Fatigue Syndrome (CFS) is a complex illness affecting 4 million Americans for which no characteristic lesion has been identified. Instead of searching for a deficiency in any single marker, we propose that CFS is associated with a profound imbalance in the regulation of immune function forcing a departure from standard pre-programmed responses. To identify these imbalances we apply network analysis to the co-expression of 16 cytokines in CFS subjects and healthy controls. Concentrations of IL-1a, 1b, 2, 4, 5, 6, 8, 10, 12, 13, 15, 17 and 23, IFN-γ, lymphotoxin-α (LT-α) and TNF-α were measured in the plasma of 40 female CFS and 59 case-matched controls. Cytokine co-expression networks were constructed from the pair-wise mutual information (MI) patterns found within each subject group. These networks differed in topology significantly more than expected by chance with the CFS network being more hub-like in design. Analysis of local modularity isolated statistically distinct cytokine communities recognizable as pre-programmed immune functional components. These showed highly attenuated Th1 and Th17 immune responses in CFS. High Th2 marker expression but weak interaction patterns pointed to an established Th2 inflammatory milieu. Similarly, altered associations in CFS provided indirect evidence of diminished NK cell responsiveness to IL-12 and LT-α stimulus. These observations are consistent with several processes active in latent viral infection and would not have been uncovered by assessing marker expression alone. Furthermore this analysis identifies key sub-networks such as IL-2:IFN-γ:TNF-α that might be targeted in restoring normal immune function.

1. Background

Chronic Fatigue Syndrome (CFS) is characterized by persistent and unexplained fatigue resulting in severe impairment in daily function and is defined by symptoms, disability, and exclusion of medical and psychiatric conditions that could explain the fatigue (Fukuda et al., 1994; Reeves et al., 2003; Prins et al., 2006). The US Centers for Disease Control and Prevention (CDC) estimates that as many as 4 million people are affected with CFS in the US alone (Reeves et al., 2007; Chandler et al., 2008). Costs to the US economy are estimated at $9.1 billion in lost productivity (Reynolds et al., 2004) and up to $24 billion dollars in health care expenditures annually (Jason et al., 2008). Furthermore complications and co-morbidity can be severe. For example, CFS is associated with chronic and episodic cardiovascular and autonomic dysfunction (Gerrity et al., 2003). Therefore this illness has far-reaching consequences and constitutes a significant public health concern.

Evidence of chronic immune dysfunction in CFS has been reported by several groups (Klimas et al., 1990; Straus et al., 1993; Hilgers and Frank, 1994; Keller et al., 1994; Tirelli et al., 1996; Gupta et al., 1997; Patarca et al., 1997; Patarca-Montero et al., 2001; Siegel et al., 2006) though the exact nature of this dysfunction remains unclear (Maher et al., 2003). A principal avenue of investigation has been the measurement in blood of immune signals conducted by cytokines. Many of the symptoms experienced by CFS patients strongly resemble the "sickness behavior" that can be induced by the administration of pro-inflammatory cytokines. In particular decreased motor activity, altered food and water intake, sleep and cognition have been linked to increases in the levels of IL-1b, IL-6 and TNF-α in the brain (Dantzer et al., 2008). Individual cytokines however are pleiotropic and their biological activities are known to be context specific. This becomes evident when considering the current body of work focused on immune dysfunction in CFS. While some studies have reported increased levels of anti-inflammatory cytokines such as IL-10 (ter

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Wolbeek et al., 2007) and IL-4 (Skowera et al., 2004), others have shown a correlation with pro-inflammatory signals TNF-α and IL-6 (Gaab et al., 2005; Carlo-Stella et al., 2006). Admittedly the heterogeneity of the CFS population (Vollmer-Conna et al., 2006; Aspler et al., 2008; Kerr et al., 2008b) has been an issue. However a major failing remains analytical. In particular immunological markers continue to be analyzed individually even though their expression is articulated as part of an integrated network. In addition to the numerical advantages of a combinatorial approach, for example the control of excessive measurement noise (Szymanska et al., 2007), it is becoming apparent that understanding complex disease will require more than a list of defective cells or genes. Because cellular and molecular components are highly inter-dependent it is necessary to understand the "wiring" via which they interact (Barabási, 2007). Immune cells form a distributed network of diverse elements that exchange information through a complex web of interactions (Orosz, 2001). The architecture of such a networked system profoundly impacts its behavior (Klemm and Bornholdt, 2005) and the strategies that are available for adapting to change and maintaining homeostasis. Nonetheless, the formal analysis of biological networks in defining disease phenotypes has received relatively little attention. Recent attempts have focused on the visual comparison of relatively sparse collections of known pathway elements (Kerr et al., 2008a) or a broad description of shifts in overall structure (Emmert-Streib, 2007). We have extended this work in several important ways, introducing continuous metrics that quantify not only the degree of change but the type of change occurring in global and more importantly in local network structure. These metrics have allowed us to identify functional communities of markers within these networks as well as key elements driving disease-related changes in network structure (Fuite et al., 2008).

Here we use network constructs such as these to examine how patterns in the coordinated expression of cytokines might differ in CFS subjects. In a recent publication we introduced the multiplex method to simultaneously measure a broad spectrum of 16 cytokines in order to assess their use as biomarkers for CFS (Fletcher et al., 2009). Using this same experimental data we have now constructed separate networks describing co-expression of these 16 cytokines in a group of CFS subjects and in a group of healthy controls, respectively. Pair-wise mutual information (MI), estimated from the biological variability within each group, was used as a robust measure of association between cytokines. These networks were then analyzed using quantitative metrics rooted in graph theory to assess the importance and nature of architectural changes related to illness. In particular we assessed local changes in the degree of connectivity at cytokine nodes and the redistribution of these connections as they form distinct and more locally centered communities. Consistent with our previous work (Fuite et al., 2008) we found that these cytokine networks differed significantly in architecture between diagnostic groups emphasizing that the organizational attributes of the immune response in addition to the activation level of individual markers constitute a unique characteristic of CFS. Of note distinct modules emerged in both healthy control and CFS networks that were recognizable as components of Th1, Th2 and Th17 responses. In CFS we found consistent but significantly attenuated patterns of Th1 and Th17 response occurring in the context of a well-established Th2 inflammatory environment. These patterns would have escaped detection had the analysis focused solely on differential expression of individual cytokines. Interestingly the cytokine co-expression patterns described in this study, though not uniquely assignable to a viral pathology, were at least consistent with the disruptive effects of latent viral infection by pathogens such as Epstein–Barr virus (EBV) (Samanta and Takada, 2009; Tsuge et al., 2001).

2. Materials and methods

2.1. Sample collection and processing

2.1.1. Subject cohort

Female CFS patients ($n = 40$; mean age 50) were from the CFS and Related Disorders Clinic at the University of Miami. A diagnosis of CFS was made using the International Case Definition (Fukuda et al., 1994; Reeves et al., 2003). Healthy female controls ($n = 59$; mean age 53) were from a NIH funded study. All CFS study subjects had a SF-36 summary physical score (PCS) below the 50th percentile, based on population norms. Exclusion criteria for CFS included all of those listed in the current Centers for Disease Control (CDC) CFS case definition, including the listed psychiatric exclusions, as clarified in the International CFS Working Group (Reeves et al., 2003). All CFS subjects were assessed for psychiatric diagnosis at the time of recruitment with the Composite International Diagnostic Instrument (World Health Organization, 1997). Based on this assessment, we excluded subjects with DSM IV diagnoses for psychotic or melancholic depression, panic attacks, substance dependency, or psychoses as well as any subjects currently suicidal. We also excluded subjects with Borderline or Antisocial Personality Disorder. Subjects had no history of heart disease, COPD, malignancy, or other systemic disorders that would be exclusionary, as clarified by Reeves et al. (2003). Subjects were excluded for the following reasons: less than 18 yrs of age, active smoking or alcohol history, history of significant inability to keep scheduled clinic appointments in past.

Ethics statement. All subjects signed an informed consent approved by the Institutional Review Board of the University of Miami. Ethics review and approval for data analysis was also obtained by the IRB of the University of Alberta.

2.1.2. Cytokine profiles

Morning blood samples were collected into ethylene diamine tetra acetic acid. Plasma was separated within 2 h of collection and stored at −80 °C until assayed. We measured 16 cytokines in plasma using Quansys reagents and instrument (Quansys Biosciences, Logan, Utah). The Quansys Imager, driven by an 8.4 megapixel Canon 20D digital SLR camera, supports 96 well plate based chemiluminescent imaging. The Q-Plex™ Human Cytokine - Screen (16-plex) is a quantitative enzyme-linked immunoabsorbent assay (ELISA)-based test where sixteen distinct capture antibodies have been absorbed to each well of a 96-well plate in a defined array. Manipulation of the range of the standard curves and exposure time allowed reliable comparisons between CFS patients and controls of both low and high level cytokine concentrations in plasma. For the standard curves, we used the second order ($k = 2$) polynomial regression model (parabolic curve): $Y_p = b_0 + b_1X_1 + b_2X_2 \ldots + b_kX_k$, where Y_p is the predicted outcome value for the polynomial model with regression coefficients b_1 to k for each degree and y intercept b_0. Quadruplicate determinations were made, i.e., each sample was run in duplicate in two separate assays. Statistics reported in Table S3 show an average coefficient of variability (CV) of 0.20 for inter-assay and 0.09 for intra-assay repeatability. Also reported in Table S3 are the lower limits of detection (LLD) for each cytokine estimated from the standard calibration curve. In many cases the standard curve yielded a negative intercept value indicating that the modified assay produced a background optical signal at zero concentration. Accordingly, the standard curves were truncated at this baseline optical intensity and no negative concentration values were estimated or used in this analysis. In the case of cytokines with positive intercept values very few samples produced results below the LLD with the exception of IL-17. While the LLD for IL-17 was lower with the modified protocol roughly

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one quarter of the CFS patients, and 1 in 10 control subjects, registered average expression values below detection.

2.2. Statistical analysis

Association networks were constructed using mutual information criteria (MI) implemented in the ARACNe software (Margolin et al., 2006a,b). The mutual information MI(X;Y) shared by X and Y corresponds to the total entropy $H(X)$ and $H(Y)$ of these variables minus their joint entropy $H(X,Y)$ (Eqs. (1)–(3)). In order to use this metric the continuous scale for the concentration of each cytokine was divided into bins defined by a set of Gaussian kernels. The optimal choice of kernel width is dependent on the sample size and the distribution statistics of the data. The algorithm used by the ARACNe platform is based on a computationally efficient estimation algorithm (Beirlant et al., 1997) and described in detail in Margolin et al. (2006a) and the Supplementary Technical Report in Margolin et al. (2006b). The null probability of each MI value was computed by sub-sampling with replacement. Subsets of 30 observations were repeatedly constructed by sampling each subject group separately. Samples were not removed from the candidate list if selected thereby making them available again for the next iteration. The final aggregate networks for each diagnostic group were generated from a consensus of 300 sub-sampled networks. Networks were stable in size over a wide range of MI significance thresholds (Supplementary Figure S1) and $p \leqslant 0.001$ was used in all subsequent computations. This was used as the threshold for MI confidence in all subsequent computations. This consensus averaging across sub-sampled data sets and the fact that MI assigns equal influence to each measured value makes this approach quite robust to outliers (Craddock et al., 2006; Butte and Kohane, 2000). Nonetheless for additional detail we have included the values for conventional Spearman rank-based cross-correlation of cytokines in Tables S4 and S5 for the healthy controls (HC) and CFS patient groups, respectively.

$$H(X) = -\sum_{i=1}^{n} p(x_i)\log(p(x_i)) \tag{1}$$

$$H(X,Y) = -\sum_{j=1}^{n}\sum_{k=1}^{m} p(x_i,y_k)\log(p(x_j,y_k)) \tag{2}$$

$$\mathrm{MI}(X;Y) = H(X) + H(Y) - H(X,Y) \tag{3}$$

Indirect associations were removed using data processing inequality (DPI) (Cover and Thomas, 2006). DPI states that if X and Z interact only through a third variable Y then Eq. (4) applies. Thus the smallest MI value can only come from indirect interaction. ARACNe removes this edge.

$$\mathrm{MI}(X,Z) \leqslant \min[\mathrm{MI}(X,Y);\ I(Y,Z)] \tag{4}$$

Topological differences in networks were evaluated using a weighted graph edit distance (Bunke, 2000) corresponding to the minimum summed "cost" associated with the removal and insertion of edges transforming one graph into the other (Dickinson et al., 2004; Harper et al., 2004). Herein we make the costs of these edit operations directly proportional to the changes in edge MI. The weighted graph edit distance, d_{GED}, between two undirected networks of order N with adjacency matrices, A and B, is computed as follows where $a_{ij} = \mathrm{MI}_{ij}$ if $P(\mathrm{MI}_{ij} > 0) \geqslant 0.001$, else $a_{ij} = 0$ and similarly for b_{ij}:

$$d_{\mathrm{GED}} = \sum_{i=1}^{N}\sum_{j\geqslant i}^{N} |a_{ij} - b_{ij}| \tag{5}$$

Significance of this edit distance was estimated (i) using reference networks generated by random sub-sampling of HC subjects, (ii) from equal-sized random networks conserving edge weight distribution (Milo et al., 2004) and (iii) through multi-graphs conserving node degree distribution (Newman, 2004b).

Node degree centrality or direct connectivity of each node i to its immediate neighborhood N_i was computed as $\sum_{j\in N_i} a_{ij}$. Eigenvector centrality x_i was also computed for each node i as a measure of that node's connectivity to its remote neighbors. For the ith node the eigenvector centrality score x_i is proportional to the sum of x_j for all nodes connected to it such that:

$$x_i \propto \sum_{j\in N_i} x_j \Rightarrow x_i = \frac{1}{\lambda}\sum_{j\in N_i} x_j = \frac{1}{\lambda}\sum_{j=1}^{N} a_{ij}x_j \tag{6}$$

where N_i is the neighborhood of i, λ is some constant and N is the order of the network. Constraining all $a_{i,j}$ and x_i to real positive values implies, by the Perron–Frobenius theorem, that only the largest principal eigenvalue solution to Eq. (6) is accepted (Kleinberg, 1999). Finally we have also scaled the principal eigenvector X to adjust for network size as follows:

$$\hat{X} = \frac{\sqrt{2}}{\|X\|}X \tag{7}$$

where $\hat{X}$ is the normalized principal eigenvector and $\|X\|$ is the norm. This scaling is based on a maximum of $x_i = 1$ for the center node of a star network (Ruhnau, 2000). The two node centralities, degree and eigenvector, are among the common numerical values that measure network connectedness to imply node reach, control, and influence within groups.

The overall degree of centralization for any network of order N and normalized principal eigenvector $\hat{X}$ is the centrality index C:

$$C_{\mathrm{eigenvector}} = \frac{\sum_{i=1}^{N}(x_{\max} - x_i)}{\sum_{i=1}^{N}(1 - x_i)} \in [0,1]. \tag{8}$$

Modularity, Q, is a measure of community structure within a network (Girvan and Newman, 2002; Newman, 2004a), Q = (fraction of edges within modules) − (fraction of edges expected within modules), such that (Newman and Girvan, 2004),

$$Q = \frac{1}{2m}\sum_{i,j=1}^{n}(A_{i,j} - P_{i,j})\partial_{g_i,g_j} \ \in [-1,1] \tag{9}$$

where m is the graph size,

$$m = \frac{1}{2}\sum_{i,j=1}^{n} A_{i,j} \tag{10}$$

n is the graph order, $A_{i,j}$ is a component of the symmetric weighted adjacency matrix describing the network, and g_i is the community to which node i is a member. The expected probability an edge randomly falls between two nodes is

$$P_{i,j} = \frac{k_i k_j}{2m} \tag{11}$$

where $k_i = \sum_{j=1}^{n} A_{i,j}$ is the degree of node i.

To split any network or sub-network on the basis of maximizing modularity, a *modularity matrix*, B, is established having elements (Newman, 2006a),

$$B_{i,j} = A_{i,j} - P_{i,j} \tag{12}$$

Elements of the leading eigenvector of the modularity matrix are used to direct a splitting of the network into two modules and to assign corresponding node membership based on sign (+/−) and magnitude (Newman, 2006b). This process was iterated

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and modules sequentially identified until a maximum modularity for the overall network was reached or until further cuts increased modularity insignificantly ($p > 0.05$).

Graphical rendering was performed using a "spring-electrical" embedding (Pemmaraju and Skiena, 2003) where nodes are idealized as similarly charged objects that repel each other. Edges are imagined as springs adhering to Hooke's law with spring-constants proportional to their MI weights. The network is relaxed iteratively to a minimum energy embedding, which naturally reveals modular structure.

3. Results

3.1. Cytokines undergo widespread differential expression in CFS

Results of the nonparametric Wilcoxon rank-sum test comparing the difference in median expression for each cytokine in CFS versus healthy control (HC) have been presented previously (Fletcher et al., 2009) and are summarized in Supplemental Table S1. Briefly these show that 10 of the 16 of the cytokines surveyed had significantly different median expression levels ($p \leqslant 0.05$) across groups. Circulating concentrations of interleukins (IL) IL-1a, 1b ($p \leqslant 0.05$) as well as 4, 5, 6, 12 and lymphotoxin-alpha (LT-α) ($p \leqslant 0.01$) were markedly higher. Conversely, CFS patients exhibited lower expression of IL-8, 13, and 15 ($p \leqslant 0.01$). Levels of IL-2, 10, 17, and 23, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) showed little difference in expression between groups. Increased levels of IL-1b and IL-6 in CFS align with experimental results showing the induction of "sickness behavior" from increased levels of pro-inflammatory cytokines (Dantzer et al., 2008) in the brain.

3.2. Altered associations are pervasive among cytokines in CFS

In order to verify the relative homogeneity of subject groups with regard to their cytokine signatures we first used a transpose of the experimental data to construct an analogous MI association network where each subject was represented by a node. The topology of the resulting network, when viewed as a low energy embedding, showed a natural separation of subjects into two non-overlapping regions consistent with the diagnostic assignment (Fig. 1 inset). As a result all subjects in each group were used in the construction of the cytokine co-expression networks for CFS and HC, respectively. Individual networks were then constructed for HC and CFS subjects using the within-group variability to estimate the pair-wise MI or shared information linking the expression of these 16 cytokines (Fig. 1). Random sub-sampling of the subject groups was conducted to establish confidence intervals for the graph edit distance between phenotypes (Figure S1). The narrow distribution of edit distance values separating within-group networks further supported the assessment that each diagnostic group was relative homogeneous in composition.

Summary statistics describing basic properties of the CFS and HC networks are shown in Table 1. Interestingly while the average number of links per node differed between networks the overall mutual information supported by these connections did not. An average node was connected to its neighbors by one additional link in the HC network, namely 5.9 versus 5.1 links in the CFS network ($p < 0.01$). Nonetheless the mutual information carried to the average node by these connections was essentially the same if we compare the cumulated link weight of 0.236 in HC to that of 0.240 in CFS ($p >> 0.05$). Although these networks were similar in terms of their overall mutual information (cumulated edge weight) or network size, they differed significantly in how this mutual information was distributed. The CFS network had a significantly higher centrality index, 0.448 versus 0.331 in HC ($p << 0.01$), suggesting a greater reliance on a minority of highly connected hubs. Accordingly a quantitative comparison of overall network topology showed that HC and CFS networks were separated by a weighted edit distance of ~1.96 (Eq. (5)) as a result of this re-structuring (Figure S1). This corresponded to more than 10 standard deviations (0.13) above the expected distance between two networks constructed from randomly sampled HC subjects ($d_{edit} \sim 0.18$) and 3 standard deviations (~0.50) above the expected separation between two randomly assembled multi-graphs ($d_{edit} \sim 0.88$) conserving node degree (data not shown).

The spring-mass representations shown in Fig. 1 confirm that these networks were visibly different in topology. This increase in overall network centrality in CFS was driven primarily by a few interacting markers. Local re-structuring was described by changes in node degree centrality, a measure of direct connectivity, and eigenvector centrality, a combined measure of direct and indirect connectivity. Results presented in Fig. 2 indicate that nodes representing IL-1b, 2, 4, IFN-γ and TNF-α concentrations became better integrated into the core network of CFS, both in terms of their association with direct and remote neighbors. Despite maintaining similar eigenvector centrality in both networks, the strength of direct connections from neighboring nodes to IL-10 substantially increased (degree centrality) in CFS. In addition,

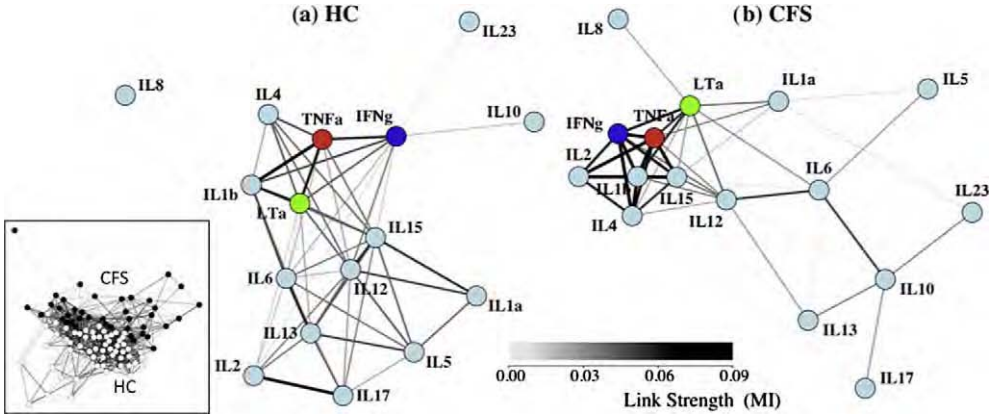

Fig. 1. Networks for HC and CFS have visibly different topologies. A weighted spring-electrical embedding structurally reveals the subject–subject (inset) and cytokine–cytokine associations based on measurements in 59 healthy control subjects (a) and 40 CFS patients (b). All edge weights are significant at $p \leqslant 0.01$. Separation of subjects was consistent with their assignment to diagnostic groups supporting the use of within-group variation in the estimation of mutual information for cytokine–cytokine associations.

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Table 1
Connectivity patterns differ significantly between groups. Summary of network-wide descriptive metrics with associated standard error () for the HC and CFS networks as well as for sub-networks I+ and II−.

Network	Metric	HC	CFS	*p*-Value
Overall network	Order (total number of nodes)	16	16	
	Mean links per node[a]	5.9 (0.2)	5.1 (0.2)	0.009
	Mean node degree[b]	0.236 (0.007)	0.240 (0.007)	0.689
	Centrality index	0.331 (0.011)	0.448 (0.006)	0.000
	Modularity index	0.398 (0.019)	0.394 (0.020)	0.978
Cluster I+	Order (total number of nodes)	8	10	
	Mean links per node	5.3 (0.2)	2.6 (0.2)	0.000
	Mean node degree	0.217 (0.008)	0.088 (0.005)	0.000
	Centrality index	0.187 (0.011)	0.609 (0.016)	0.000
Cluster II−	Order (total number of nodes)	8	6	
	Mean links per node	2.8 (0.2)	5.0 (0.0)	0.000
	Mean node degree	0.121 (0.005)	0.332 (0.002)	0.000
	Centrality index	0.562 (0.012)	0.112 (0.002)	0.000

[a] Mean links per node counts all links with non-zero weight as 1 link.
[b] Mean node degree uses the link weight or MI value.

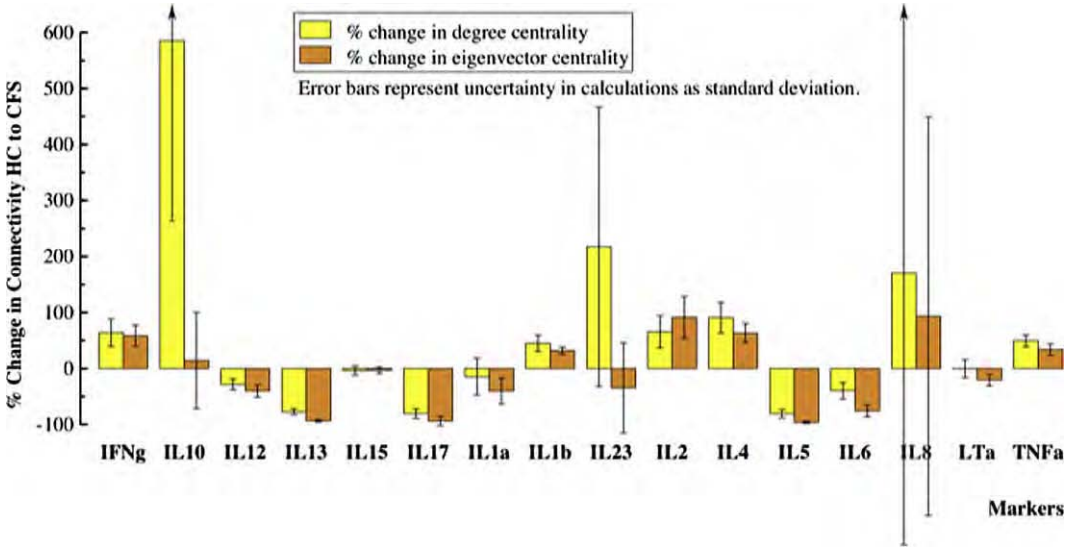

Fig. 2. Most cytokines significantly modified their connectivity in the CFS state. Theses network alterations were revealed by the relative change in the total weight of edges connected at each node (node degree centrality) as well as edges acquired through first neighbors (normalized eigenvector centrality). Interleukins (IL), 2, 4, and 1b, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) became much better integrated into the core network in CFS, while interleukins, 5, 6, 12, 13, and 17 became more weakly associated.

IL-10 shifted from having a weak association to a core node (IFN-γ) in HC to having stronger associations to an opposite group of nodes in CFS (IL-6, 13, 17, 23) (Figs. 2 and 3). Markers that were much less strongly connected in CFS were IL-5, 6, 12, 13, and 17 (Table S1). By the same token cytokines IL-8, 15, and 23 remained unchanged in their degree of overall integration in the CFS and HC networks.

3.3. Mid-scale shifts in network structure

The distribution of connections in each network among sets of nodes suggested that both the HC and CFS networks were made up of sub-networks. To analyze the extent of community structure within each network we iteratively divided the set of cytokine nodes into subsets and calculated increase in overall network modularity. Results indicated that the extent of community structure in the HC and CFS networks was about the same with maximal modularity values of 0.398 and 0.394, respectively. These values were achieved when the networks were broken down into two component modules, labeled I+ and II− (Table 1, Fig. 3). Separation into additional modules either lead to a decrease in modularity, or did not significantly increase the modularity index at $p < 0.05$ confidence.

Results in Table 1 show that although both HC and CFS networks were made up of two mid-scale communities; these constituent modules possessed important differences in internal structure. Cluster I+ became less densely linked in among CFS patients as measured by a significant decline in number and strength of internal node associations. In cluster I+ of the CFS network the mean number of links per node fell from 5.3 to 2.6 ($p < 0.01$) and the mean node degree fell from 0.217 to 0.088 ($p < 0.01$). In addition cluster I+ became structurally more hub-like in CFS with an increase in centrality index to 0.609 from 0.187 in HC ($p < 0.001$). Conversely cluster II− became structurally less focused in CFS dropping in centrality index from 0.562 to 0.112 ($p < 0.001$). More evenly connected, cluster II− was also more densely linked in CFS patients with significant increases in the number and strength of internal node associations. The mean number of links per node rose from 2.8 to 5.0 ($p < 0.01$) in cluster II−, and the mean node degree increased from 0.121 to 0.332 ($p < 0.01$) in the CFS network.

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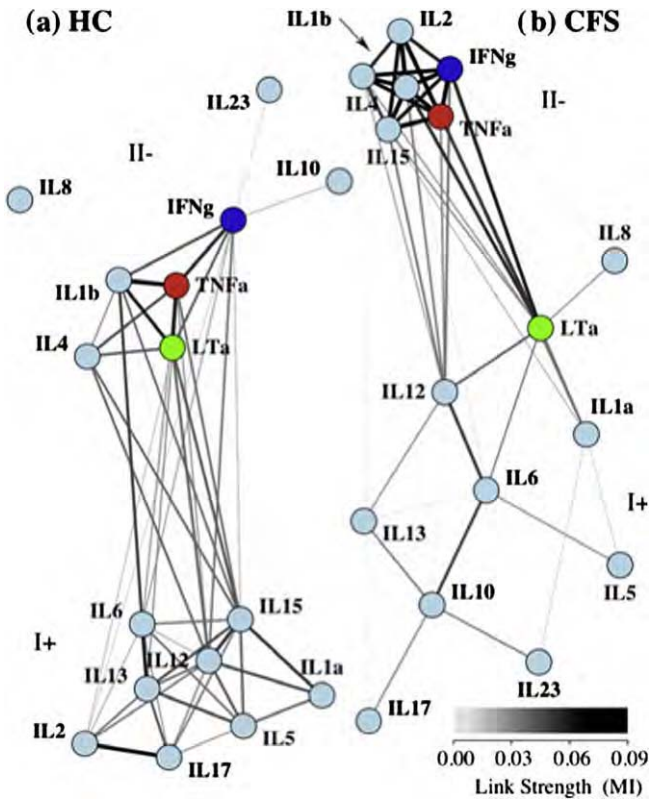

Fig. 3. Both HC and CFS networks are composed of two distinct communities. Visually "relaxing" the links between identified communities of nodes and allowing them to drift apart emphasizes community structure in both networks. Overall modularity was maximized when each network was separated into two communities with differing compositions, labeled I+ at the top and II−. Each community represents a clustering of nodes with a greater internal linkage than would be expected compared to a random sampling of similar nodes.

Table 2
Cytokines change community membership in CFS. Membership score with standard error () to either of the two modules, I+ or II− for each cytokine node in HC and CFS networks. The magnitude of the membership score indicates the strength with which nodes are associated to the module they belong. Change in modularity membership score tracks differences in community association for each marker.

Marker	Module membership		Change in membership	*p*-value
	HC	CFS		
IL-1a	0.17 (0.09)	0.04 (0.06)	−0.13 (0.15)	0.004
IL-1b	−0.34 (0.04)	−0.28 (0.04)	0.06 (0.07)	0.002
IL-2	0.24 (0.06)	−0.36 (0.02)	−0.60 (0.07)	0.000
IL-4	−0.24 (0.03)	−0.29 (0.04)	−0.05 (0.07)	0.010
IL-5	0.33 (0.04)	0.13 (0.03)	−0.19 (0.07)	0.000
IL-6	0.11 (0.09)	0.41 (0.03)	0.30 (0.11)	0.000
IL-8	−0.07 (0.09)	0.02 (0.01)	0.10 (0.10)	0.176
IL-10	−0.04 (0.01)	0.41 (0.04)	0.46 (0.05)	0.000
IL-12	0.13 (0.06)	0.17 (0.05)	0.04 (0.11)	0.199
IL-13	0.28 (0.03)	0.23 (0.05)	−0.05 (0.09)	0.028
IL-15	0.05 (0.04)	−0.24 (0.03)	−0.30 (0.07)	0.000
IL-17	0.36 (0.03)	0.12 (0.03)	−0.24 (0.06)	0.000
IL-23	−0.03 (0.04)	0.15 (0.03)	0.17 (0.06)	0.000
IFN-γ	−0.29 (0.03)	−0.26 (0.03)	0.03 (0.07)	0.082
LT-α	−0.30 (0.04)	0.03 (0.04)	0.33 (0.08)	0.000
TNF-α	−0.42 (0.02)	−0.29 (0.01)	0.13 (0.03)	0.000

In addition to changes in structure we also observed changes in the composition of modules. The membership of an individual node to its respective module was measured by its centrality within the modularity matrix. This shifted significantly in CFS as a result of changing pair-wise associations (Table 2). In CFS the markers IL-10, IL-23 and LT-α shifted from cluster II− to cluster I+. While IL-6 strengthened its position in cluster I+ of the CFS network it shed the direct and strong association it held with IL-1b in HC. Conversely the markers, IL-2 and IL-15 moved in the opposite direction, significantly shifting centrality away from cluster I+ and towards cluster II− in CFS. These changes in centrality were significant at $p < 0.001$. In contrast IL-8 maintained marginal association with either of these node communities in both CFS and HC.

4. Discussion

In order to explore changes in the patterns of immune activity in CFS we constructed two distinct association networks linking the expression of 16 cytokines measured in plasma for 40 female patients and 59 case-matched healthy controls (HC). Quantitative analysis of these two networks indicated that their topologies differed far beyond what would be expected by chance alone. Indeed variation separating the patterns of cytokine–cytokine association from each subject group was 10 times greater than the variability found within each group. Interestingly the average cytokine node in either network supported the same overall exchange of mutual information. This being said a typical CFS network node relied on one less connection to do so. This is an important point as it suggests that despite differences in cytokine expression between groups both networks were equally coherent overall ($p = 0.689$, Table 1). Even at the basal levels of cytokine expression found in the HC group the correlation linking cytokines into a network was not only significant (all edges $p < 0.001$) but it was virtually equivalent to the overall strength of association supporting the CFS network. Instead the difference between CFS and HC networks arose from a redistribution in the routing of mutual information with the CFS network relying more strongly on a minority of highly connected hubs. Driving these changes in structure we found that cytokines IL-1b, 2, 4, IFN-γ, TNF-α became much better integrated into the core CFS network, so much so that these formed a distinct sub-network. Direct connections to anti-inflammatory cytokine IL-10 also increased substantially in CFS while the reverse was true of IL-13, 17 as well as IL-5 and 6. Despite this local re-structuring these very different cytokine networks still shared a similar overall granularity. Using a novel measure of modularity we dissected these cytokine networks and found that two mid-scale communities could be isolated in both the CFS and HC group: clusters I+ and II−. However a closer look at the internal structure of these communities revealed diametrically opposite designs across illness groups. In CFS cytokine nodes in cluster I+ were more sparsely connected and adopted a more hub-like architecture whereas cytokine nodes in cluster II− were more strongly and more uniformly interconnected. The exact opposite is true of these same clusters in the control network. Differences such as these reinforce the notion that CFS manifests not only as a difference in the expression level of individual cytokines but also as an important shift in the patterns of association linking these cytokines.

The emergence of a tight-knit cluster dominated by Th1 cytokines was perhaps the most significant and most visible feature of the CFS network. Consisting of cytokine nodes IL-1b, IL-4, IFN-γ and TNF-α cluster II− also saw the recruitment of cytokines IL-2 and IL-15 from their position in cluster I+ of the HC network. This group became much more tightly associated in CFS and less centered about any individual cytokine. Interestingly IL-2, 4 and 15 belong to a family of cytokines that also includes IL-7, IL-9 and IL-21. Members of this family share a receptor complex consisting of IL-2 specific IL-2 receptor alpha (CD25), IL-2 receptor beta (CD122) and a common gamma chain (γc). It is not surprising therefore to observe a strong association between these network nodes upon immune activation. IL-2 and IL-4 are both T cell growth

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factors though the latter is a much more effective promoter of B cell proliferation (Burke et al., 1997). In these data, the IL-4 median concentration was increased 3-fold in CFS while IL-2, IFN-γ and TNF-α concentrations remained unchanged. This would support the presence of an active Th2 component in CFS and an antagonistic role for IL-4 towards Th1 cytokines such as IFN-γ within cluster II−. Additionally new recruits, IL-2 and IL-15, both contribute to NK cell proliferation. Though NK cell response was not assessed directly in this work, the lower levels of IL-15 and unchanged levels of IL-2 observed here appear consistent with reports of deficient NK cell response in CFS (Maher et al., 2005).

Contrary to cluster II−, cluster I+ was dominated by cytokines typically associated with innate immunity and/or Th2 adaptive response namely IL-5, 6, 10, 12 and 13. For the most part associations between cytokine nodes in cluster I+ were fewer in number and visibly weaker than those linking their counterparts in cluster II−. Despite having weaker ties the circulating levels of IL-5, IL-6 and IL-1a were significantly elevated suggesting an established Th2 inflammatory environment. Indeed in CFS the mean node degree within cluster I+ was 4-fold lower than that of cluster II− (Table 1) and the centrality index 6-fold higher suggesting a much sparser and more centrally directed pattern of interaction. Especially recognizable in CFS cluster I+ is the relatively strong association of pro-inflammatory cytokine IL-6 with anti-inflammatory counterpart IL-10. Recall that IL-10, though not differentially expressed, shifted from having a weak association with cluster II− in the HC network to this much more central role in cluster I+ opposite IL-6 in CFS. This altered role would have gone unnoticed in a more conventional analysis. Also recognizable are elements of the IL-23/Th17/IL-17 response (Boniface et al., 2008; Aggarwal et al., 2003; McGeachy et al., 2007). The direct antagonism of IL-17 response by IL-2 (Laurence et al., 2007) observed in the HC network was absent in CFS. Instead an alternative response emerged whereby IL-17, IL-23 and IL-6 were all separated by IL-10. IL-6 typically enhances IL-1b–driven IL-17 production (Louten et al., 2009; Perona-Wright et al., 2009) while IL-10 is known to effectively down-regulate Th17 cytokine expression in macrophages and T cells (Gu et al., 2008). In these data median concentrations of IL-17 and 23 were unchanged despite elevated levels of IL-1b and IL-6. Though Th17 activation was not measured directly these observations suggest that responsiveness of this subset, like that of NK cells, may be altered in CFS.

Another key feature of the CFS network is the central role that the hub nodes LT-α and IL-12 (Fig. 3b) play in linking cytokine clusters I+ and II−. In contrast this role is almost evenly shared between IL-6, IL-15 and IL-2 in the HC network. No longer a member of cluster II− in CFS, the LT-α hub nonetheless maintains strong associations to IL-1b, TNF-α and IFN-γ. Primarily a product of activated T and B-lymphocytes, LT-α shares a strong homology with TNF-α and IL-1b and is a powerful inducer of both these cytokines (Kasid et al., 1990). Moreover IFN-γ has been shown to increase the number of receptors for TNF-α and LT-α further promoting their action (Aggarwal et al., 1985). In opposition to this, IL-4 will inhibit IL-2 triggered production of TNF-α and LT-α in mixed PBMC populations (Kasid et al., 1990). The network links identified here indicate that these known responses of IL-1b and TNF-α to LT-α, and to a lesser extent IFN-γ, remained consistently expressed in the data. However, while the expression of IL-1b increased 2-fold in CFS, that of TNF-α remained unchanged despite an almost 4-fold increase in LT-α. This attenuated TNF-α response in CFS could in principle be linked with the absence of IFN-γ engagement and the elevated levels of IL-4 (>3-fold) observed in these patients. In comparison to LT-α, the association of IL-12 with the nodes of cluster II− is much weaker. Typically released by macrophages and dendritic cells, IL-12 is known to stimulate the production of IFN-γ and TNF-α from NK and T cells. This effect is enhanced by IL-2 (Wang et al., 2000) and to a lesser extent by IL-4 (Bream et al., 2003), a cytokine normally suppressive of IFN-γ production. Though elevated 2-fold in this CFS cohort, the absence of a concordant IFN-γ response further supports a dampened sensitivity of NK cells to IL-12 signaling in CFS. This may be due at least partially to inadequate IL-2 priming of IL-12 receptor expression (Wang et al., 2000) since IL-2 concentrations remained unchanged.

Viral triggers such as EBV and human cytomegalovirus (HCMV) have long been suspected of involvement in the onset and persistence of CFS. Recent evidence of xenotropic murine leukemia virus-related virus (XMRV) involvement in CFS (Lombardi et al., 2009) further supports this hypothesis. While other causes may underlie the cytokine expression patterns observed in this work many of these are at least consistent with some of the disruptive effects of chronic viral infection. In one potential model, infection with one or several viral agents may trigger or exploit deficient responsiveness of NK cells to IL-12 and LT-α, both of which are actively produced by EBV-immortalized B cells (Airoldi et al., 2002; Thompson et al., 2003), leading to impaired IFN-γ production and Th1 activation. In this scenario increased IL-6, also produced by EBV-infected B cells, together with depressed levels of IL-15 may interfere with LT-α and IL-12 activation of NK cells and the resulting IFN-γ production (Wilson et al., 2001; Saghafian-Hedengren et al., 2009). It is important to note however that while many of the patterns found here aligned with known EBV processes others did not; for example the lack of elevated IL-10 (Samanta et al., 2008) and IL-13 (Tsai et al., 2009). As very distinct illnesses arise from the expression of specific subsets of the 12 known EBV induced genes (Tsuge et al., 2001) the notion that CFS may involve a form of restricted viral latency may be worthy of consideration. Finally from a methodological perspective we observed that several significant shifts in network structure involved cytokines that were not differentially expressed across subject groups. This underscores the significance of co-expression analysis in understanding complex illnesses such as CFS. In particular such an analysis makes it possible to detect low-grade immune processes that may operate consistently with relatively modest changes in marker expression.

Authors' contributions

Conceived and designed the experiments: M.A.F., N.G.K., G.B. Performed the experiments: M.A.F., N.G.K. Analyzed the data: J.F., A.K., G.B. Contributed reagents/materials/analysis tools: M.A.F., A.K., G.B., J.F. Wrote the paper: G.B., M.A.F., J.F., A.K., S.D.V., N.G.K.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbi.2010.04.012.

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Reply to Letter to the Editor

Circadian rhythms in cytokine secretion in chronic fatigue syndrome

Dear Dr. Carlo-Stella,

Thank you for your interest in our research and your kind words of encouragement. We completely agree with your comments regarding the importance of circadian rhythm and sleep abnormalities in chronic fatigue syndrome (CFS). Indeed in one of our early efforts as a group we found that heart rate variability (HRV) during sleep was a key clinical variable that aligned strongly with characteristic gene expression patterns in distinguishing female CFS patients from control subjects (Broderick et al., 2006). Thank you also for raising the issue of altered regulatory dynamics in CFS. This has in fact been one of our basic models for describing CFS and similar complex illnesses such as Gulf War syndrome (GWS). In recent work we used a computational model to show that the stress response axis can support more than one set of regulatory dynamics by virtue of its very design (Ben-Zvi et al., 2009). As a result we certainly agree that ignoring the dynamics of homeostatic regulation and diurnal cycles can lead to erroneous interpretations. In an attempt to avoid this pitfall we controlled for circadian rhythm by conducting patient assessment and sample collection at the same time of day for all subjects throughout the study. Had funding been available to conduct a time course study we would have pursued this avenue enthusiastically. While static snapshots, even synchronized, do not offer a complete description of illness processes they can nonetheless deliver important insight if considered in the proper context. We believe the current article to be a valuable first step in establishing such context. The notion of context is implicit in the analysis of co-expression patterns and delivers insight unavailable from the conventional comparison of individual cytokine concentrations. Indeed several key network nodes were associated with cytokines that did not change in expression across patient groups. One could also argue that since these networks describe associations they necessarily incorporate some of the information from trends in cytokine expression. Admittedly this information would apply only to a narrow window in time. In the end a formal time course study, preferably one that spans two or more days, will be required to provide a complete description of illness-related changes in circadian dynamics. In keeping with this, much of our ongoing work is focused on novel methods for describing how these association networks change in structure over time as well as across patient groups. We are currently developing such methods using concepts rooted in network theory and applying them to time course data describing immune and endocrine response to exercise in CFS and GWS. Initial results are encouraging and we hope to report these shortly.

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Ben-Zvi, A., Vernon, S.D., Broderick, G., 2009. Model-based therapeutic correction of hypothalamic–pituitary–adrenal axis dysfunction. PLoS Comput. Biol. 5 (1), e1000273 (Epub Jan 23).

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Appendix E: Proceedings

1) Yang C, Vernon SD, Broderick G. 2009. Cognitive Performance in a Population-based Cohort of CFS Patients. Poster presentation. 95th Annual Clinical Congress, American College of Surgeons, Chicago, IL, Oct. 11-15.

2) Broderick G, Fletcher MA, Vernon SD, Klimas N, 2009, Isolating Characteristic Immune Signals under Challenge in Gulf War Illness. Int Assoc CFS/ME, Reno, NV, March 12-15: Oral session Abstracts/ Latest Research in Immunology, abstract #3.

3) Broderick G, Fuite J, Fletcher MA,Vernon SD, Klimas N, 2009, Remodeling of Lymphocyte-cytokine networks in Gulf War Illness under Challenge. Int Assoc CFS/ME, Reno, NV, March 12-15: Poster Abstracts/ Latest Research in Immunology, poster abstract #1.

Appendix F: Nancy Klimas, M.D. Curriculum Vitae

CURRICULUM VITAE

1. **Date**: July 2010

2. **PERSONAL:**

2a. **Name**: Nancy Grace Klimas

2b. **Home Phone**:

2c. **Home Address**:

2d. **Citizenship**: US

2e. **Visa Type**: None

2f. **Non-Academic Employment**: None

2g. **Military Service**: None

3. **ACADEMIC EMPLOYMENT:** University of Miami Miller School of Medicine, Department of Medicine

3a. **Office Address**: VA Medical Center (111-I)
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3b. **Office Phone**: (305) 575 3267

3c. **Current Academic Rank**: Professor, tenured

3d. **Primary Department**: Medicine

3e. **Academic Appointments**:

1996 - present: Professor of Medicine, University of Miami Miller School of Medicine, Miami, FL (primary)
1997 - present: Professor of Psychology, University of Miami College of Arts and Sciences
1999 – present: Professor of Microbiology and Immunology, University of Miami Miller School of Medicine
1987 - present: Director of AIDS Research, and Co-Director of the AIDS Clinical Research Unit, Miami VA Medical Center
1999 – present: Director, CFS/GWI Multidisciplinary Research Center (initially funded by NIH U01 AI45940)
1985 - present: Co-Director, E.M. Papper Clinical Immunology Laboratory, Division of Rheumatology and Immunology, Department of Medicine, University of Miami School of Medicine
1987 – present: Director, University of Miami Diagnostic Allergy and Immunology Clinic
2000 – present, 1985-1993; Director, VA Allergy Clinic
2001 – 6 month sabbatical, Centers for Disease Control and Prevention, National Center for Infectious Diseases/ Division of Viral and Rickettsial Diseases, Viral Exanthems and Herpesviruses Branch, "Emperic Case Definition of CFS" working group.
1998 – 2000: Director, West Palm Beach VAMC Allergy Clinic
1991 - 1996: Associate Professor of Medicine, University of Miami School of Medicine
1994 - 1999: Associate Professor of Microbiology and Immunology, University of Miami School of Medicine,
1993 - 1997: Associate Professor of Psychology, University of Miami College of Arts and Sciences
1985 - 1991: Instructor and Assistant Professor of Medicine, University of Miami School of Medicine
1986 - Coordinator, Miami VA Medical Center AIDS Program

1984 - National Cancer Institute Research Fellow; Clinical Immunology Lab, Department of Medicine, University of Miami School of Medicine

4. **HIGHER EDUCATION**

4a. **Institutional**:

Virginia Commonwealth University 9/1972 - 6/1973

University of South Florida, 9/1973 - 6/1976

University of Miami, M.D., 8/1976 - 6/1980

Baylor University Hospitals and Clinics, Medical Internship, 6/1980 – 6/1981

University of Miami Hospitals and Clinics, Medical Residency, 6/1981 – 6/1983

NCI Fellow; Post-Doctoral Fellowship in Diagnostic Laboratory Immunology, E.M. Papper Laboratory of Clinical Immunology, University of Miami, 6/1983 - 6/1984.

5. **PROFESSIONAL ACTIVITIES**

5a. **Certification, Licensure**:

National Boards Part I, II and III

Florida State Medical License, 1983- current (ME41879)

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5b. **Publications**

Books and Monographs Published:

1. Chronic Fatigue Syndrome, P. Goodnik and N.G. Klimas, eds., American Psychiatric Press, Washington, D.C., 1993.

2. Clinical Management of Chronic Fatigue Syndrome, N. Klimas, MD and R Patarca, MD PhD, eds., The Haworth Medical Press, New York ● London ,1995

3. Disability and Chronic Fatigue Syndrome. Clinical, Legal and Patient Perspectives. Klimas, N.G., Patarca, R, eds Haworth Press, Inc., New York ● London, 1997

Books currently contracted:

Chronic Fatigue Syndrome: A Patient's Guide Johns Hopkins Press; Nancy Klimas, MD

Invited Book Chapters Published:

1. Fletcher, MA, Klimas NG, Cytotoxic Lymphocytes. G. Fink, ed.. In Encyclopedia of Stress., 2nd edition, Academic Press, Oxford, 2007

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145. Krieg RE, Klimas NG, Attanasio R. Absence of an antibiotic effect of Mycobacterium ulcerans. Int J Lepr Other Mycobact Dis. 1975 Jul-Sep;43(3):265-6.

Article in popular press:

Klimas, NG Klimas, NG. "**Wake-Up Call**. **Hopeful new research shows that chronic fatigue syndrome may have a genetic basis"**. Ms. Magazine, summer issue, 2006.

INVITED LECTURES (LAST 10 YEARS)

Advances in our Understanding of Chronic Fatigue Syndrome, Pri-Med conference Ft Lauderdale Florida Feb 2010

Treatment based on pathogenesis – advances in our understanding of CFS, Fatigue Sciences Conference Calgary Canada Sept 2009

Keynote address (opening) **"Immunology of Fatiguing Disorders"** 3rd International Conference on Fatigue Science, Okinawa, Japan September 3rd, 2008

Keynote Address **"Research Advances in CFS and ME"** Canadian Conference on Fatigue and Illness, Calgary, Alberta Nov 12, 2008

"Biomarker Discovery in CFS" 8th annual TMJ Conference Rockville, MD, May 12, 2008

"Research Advances in CFS/ME" Invited lecture Western Pharmacologic Association Kona, Hawaii Jan 29, 2008

Keynote address: **Understanding the interactions of the Immune system and the brain in CFS;** International CFS/ME Clinical Conference, Oslo, Norway October 8, 2007

Evidence Based Treatment Approaches in CFS/ME; International CFS/ME Clinical Conference, Oslo, Norway October 8, 2007

Advances in our understanding of the immunology of CFS Keynote 2ndInternational Conference on ME/CFS Biomedical Research, May 25, 2007 Edinburgh, Scotland.

Diagnosis and Management of CFS, Feb 23, 2007 PRIMCARE conference Ft Lauderdale FL,

Research Updates, ME/CFS February, 2007, Madrid and Barcelona, Spain, Universad de Catilonia, series of talks to clinicians and patients "

Presidential Address, "**New Directions in CFS/ME Research"** IACFS/ME 8th annual International Research and Clinical meeting, Ft. Lauderdale, FL January 12, 2007.

The Diagnosis and Management of ME/CFS, a series of 10 talks to professionals and patients, across the country September, 2006, New Zealand

The Immunology and Genomics of Gulf War Illness – August 14, 2006 GWI Research Advisory Council, Washington, DC

Research Methodology in Fatiguing Illnesses Keynote Address Aviano, Italy: 1st International Meeting on Chronic Fatigue Syndrome and Cancer-related Fatigue_May 5th 2006

Chronic Fatigue Syndrome: From Genomics to Treatment: Keynote Address, Connecticut ME Association Regional Conference, April 30, 2006 Hartford CT

CFS In the Veteran Population: Best Practices in the Continuum of Care: Management of Infectious Disease Little Rock AR.April 26, 2006

Clinical Management of CFS - PANDORA Conference, West Palm Beach, FL Oct 27, 2005

Research Advances in CFS – **Keynote Address** , OFFER Regional Conference, Salt Lake City ,Utah 4/16/05

Impact of Research Advances on Clinical Management of CFS – Keynote, OFFER Patient Conference, Salt Lake City, Utah 4/16/05

Research Advances in CFS – **Keynote Address** , CFIDS Asso Regional Conference, Charlotte, NC Nov 13, 2004

Gene Array Technology in CFS – the C^3 Computational Challenge, Cold Spring Harbor, Oct 2005

Immunomodulatory therapies – **a review**, South Florida Allergy Journal Club, 11/04

CFS – advancing knowledge impact on management, **Keynote,** AACFS Intl Clinical Conference, Madison Wisconsin 10/04

CFS Pathogenesis Keynote address, Specialisation Course on Fibromialgia and Chronic Fatigue Syndrome International University of Catalonia Barcelona, Spain May 29, 2004. Honorary degree awarded.

Management of CFS Keynote Address, PANDORA Providers and Patient Conference, Ft Lauderdale Fl. May 11, 2004

The Diagnosis and Management of CFS NMA 2003 Annual Convention and Scientific Assembly, Philadelphia, August 2003

Immune Methodologic Issues, invited speaker NIH CFS Methodology Workshop June 2003, Bethesda, MD

CFS and Fibromyalgia – Diagnosis and Management NPACE, May 2003 Orlando Fl

CFS: What we know, what we need to know, and how to get there. New Jersey Medical Association, New Brunswick. May 2003

CFS: What we know, what we need to know, and how to get there., Regional Primary Care Conference Salt Lake City May 2003

CFS – Somatic or Physical? A Debate, Intl Behavioral Medicine Asso, Helsinki, Finland August 2002

Instruments and Design of an Empiric Case Definition Study, CDC CFS Case Definition Workshop, Calloway Gardens, May 2002

Diagnosis and Management of CFS, National American Medical Women's Association Conference, San Antonio, TX Jan 2002

Inclusion and Exclusion Criteria, CDC CFS Case Definition Workshop, Calloway Gardens, May 2001

Immunology of Chronic Fatigue Syndrome, State of the Science Meeting, NIH, October 2000

Current Understanding of CFS Pathogenesis, NIH/CFS Research Priorities Series – Autonomic Dysfunction Conference, October 2000; Neuroendocrine Abnormalities, February 2001; Immunology Conference October 2001

Immune Restoration Post Antiretroviral Therapy, Guest lecturer, Hollywood Memorial Hospital; Baptist Hospital; Mercy Hospital; Broward General Hospital; VAMC, Nashville Tennessee; Mobile, Alabama; Key West Florida; Jan – April 2005

Global Impact of HIV on Women, National Organization for Women's Global Women's Health Conference, Washington DC June 2001

Housestaff lectures (given regularly throughout all academic years): Anaphylaxis; Asthma; Immune Modulatory Therapies; Global Impact of HIV; Immune restoration in HIV infection; Hepatitis C; Hepatitis C; HIV Co-infection; Death and Dying – the Clinician's role; Chronic Fatigue syndrome; Gulf War Syndrome; Psychoneuroimmunology; Stress and Disease.

Graduate Studies Lectures: Multidisciplinary Clinical Research; Immunology 101; Psychoneuroimmunology and disease; Pathogenesis of HIV/AIDS; Chronic Fatigue Syndrome

Undergraduate Lectures: Careers in clinical research, Death and Dying

A. Other Works and Publications

Letters to the Editor

1. Klimas, N.G. and Fletcher, M.A. Chronic Fatigue Syndrome. JAMA, 1991.

2. Klimas, N.G., Blaney, N., Morgan, R. and Fletcher, M.A. Methadone and Immune Function, Amer. J. Med. 92:114-115, 1991.

Editorials

1. Klimas, N.G. and Patarca, R. The birth of a journal. J. Chronic Fatigue Syndrome. 1:1-2, 1995.

Abstracts and Presentations at National and International Meetings

1. Klimas, N.G., Lo, H., Brunschwig, J.P., Caldwell, K.E., Latif, Z.A., and Fletcher, M.A. Biochemical Morphological and Receptor Properties of Erythrocyte Glycoproteins, Soc. Complex Carbohydrates, 1980.

2. Klimas, N.G., Caldwell, K.E., Latif, Z.A. and Fletcher, M.A.: A Purified Erythrocyte Bovine Glycoprotein Useful In The Serodiagn of Infectious Mononucleosis. Clin. Res. 29 No. 5, 1981.

3. Scott, G.B., Parks, W.P., Fischl, M., Fletcher, M.A. and Klimas, N.G.: Acquired Immunodeficiency Syndrome in Haitians: A Household Approach. Presented to the Cold Spring Harbor Special AIDS Meeting. Cold Spring Harbor, New York, September 17, 1983.

4. Klimas, NG. and Fletcher, M.A: Elevation of "Forssman-like" Antibody in AIDS. Clin. Res. 42:350, 1984.

5. Fischl, M.A., Klimas, N. G., Wang, G., Georgiades, J.A., Spira, T. and Fletcher, M.A. Human -lymphoblastoid Interferon in the Treatment of Kaposi's Sarcoma, Internatl. Interferon Conf., Frankfurt, 1984.

6. Baron, G.A., Klimas, N.G., Fischl, M. and Fletcher, M.A.: Decreased Natural Cell Mediated Cytotoxicity (NCC) to Cell-Line K562 per Leu 11 Positive Cells in Acquired Immunodeficiency Syndrome (AIDS). Fed. Proc. 44:593,1985.

7. Fischl, M.A., Dickinson, G., Scott, G., Klimas, M.A., Fletcher, M.A. and Parks, W.: Evaluation of Household Contacts of Adult Patients with the Acquired Immunodeficiency Syndrome, lst Internatl. Conf. on AIDS, Atlanta, 1985.

8. Fischl, M.A., Ahn, Y.S., Klimas, N.G., Harrington, W.J. and Fletcher, M.A.: Use of Danozol in Autoimmune Thrombocytopenia Associated with the Acquired Immunodeficiency Syndrome. lst Internatl. Conf. on AIDS, Atlanta, 1985.

9. Baron, G.A., Klimas, N.G., Fischl, M.A. and Fletcher, M.A.: Natural Cell Mediated Cytotoxicity (NCC) to Cell Line K562 per Leu 11 Positive Cell is Decreased in the Acquired Immunodeficiency Syndrome. lst Internatl. Conf. on AIDS, Atlanta, 1985.

10. Klimas, N.G., Torres, 0., Silveira, G., Fischl, M.A. and Fletcher, M.A.: Humoral Immune Abnormalities in Two South Florida Acquired Immunodeficiency Syndrome Risk Groups. lst Internatl. Conf. on AIDS, Atlanta, 1985.

11. Scott, G.B., Fischl, M.A., Klimas, N.G., Fletcher, M.A., Dickinson, G. and Parks, W.: Mothers of Infants with the Acquired Immunodeficiency Syndrome (AIDS : Outcome of Subsequent Pregnancies. lst Internatl. Conf. on AIDS, Atlanta, 1985.

12. Klimas, N.G., Lian, E., Fischl, M.A. and Fletcher, M.A.: Apparent False Positive ELISA Tests for HTLV/LAV Antibody (AB) and Polyclonal B cell Activation (PCBA) in Acquired Immunodeficiency Syndrome (AIDS) Risk Groups. 2nd Internatl. Conf. on AIDS, Paris, 1986.

13. Fischl, M.A., Dickinson, G.M., Scott, G.B., Klimas, N.G., Fletcher M.A. and Parks, W.: Heterosexual and Household Transmission of the Human T-lymphotropic Virus Type III. 2nd Internatl. Conf. on AIDS, Paris, 1986.

14. Klimas, MA., Lubs, M. and Fletcher, M.A. Complement (C') Activation and Immune Complex (IC Formation in Asymptomatic Women with Multiple Miscarriages. 6th International Congress of Immunology, Toronto, 1986.

15. Fletcher, M.A. and Klimas, N.G. Polyclonal B cell activation (PBA) and the Incidence of Antibody to HTLVIII/LAV (AB) in Groups at Risk for Acquired Immunodeficiency Syndrome (AIDS). 6th International Congress of Immunology, Toronto, 1986.

16. Baron, G.C., Klimas, N.G., Ashman, M.A., Fischl, M.A. and Fletcher, M.A.: Immune Parameters of Patients with AIDS/Kaposi's Sarcoma During Human Lymphoblastoid Interferon Treatment. 3rd International Congress on AIDS, Washington, D.C., 1987.

17. Dodds, S., Fletcher, M.A., P.O'Hearn, Cole, P., Caralis, P., Klimas, N.G., et al,: Inter- and Intra- Personal Factors in the Recruitment and Retention of Subjects For an AIDS Intervention Research Study. 3rd International Congress on AIDS, Washington, D.C., 1987.

18. Baron, G.C., Bouguignon, L.Y.W., Klimas, N.G., Fischl, M.A., Scott, G.B. and Fletcher, M.A.: Reduced Lymphocyte Cap Formation in Patients with AIDS and ARC. 3rd International Congress on AIDS, Washington, D.C., 1987.

19. Tarsis, S.L., Klimas, N.G., Baron, G.S., Ashman, M.A. and Fletcher, M.A.: Decreased Natural Killer Cell Activity and Changes in T Lymphocyte Surface Markers in Patients with Chronic Epstein Barr Virus (EBV Infection. 5th Annual Medical Laboratory Immunology Conference, Williamsburg, VA, 1987.

20. Eisdorfer, C., Szapocznik, G. Scott, Fletcher, M.A., Klimas, N.G., Fordyce-Baum, M. The Biopsychosocial Research Center on AIDS: A Multidisciplinary Approach to the Investigation of the AIDS Disease. 3rd International Congress on AIDS, Washington, D.C., 1987.

21. Fletcher, M.A., Caralis, P., Laperrier, A., Ironson, G., Klimas, N,G., Perry, A., Ashman, M. and Schneiderman, N. Immune Function and Aerobic Training as a Function of Anti-HIV Status in Healthy Gay Males, 4th International Conference on AIDS, Stockholm, Sweden, June, 1988.

22. Fletcher, M.A., O'Hearn, P., Ingram, F., Ironson, G., Laperrier, A., Klimas, N.G. and Schneiderman, N. Anticipation and Reaction to Anti-HIV Test Results: Effect on Immune Function in an AIDS Risk Group. 4th International Conference on AIDS, June, 1988.

23. Fletcher, M.A., Ironson, G., Caralis, P., Laperrier, A., Klimas, N.G., O'Hearn, P., Antoni, M. and Schneiderman, N. A Behavioral Intervention Study in Anti-HIV Positive and Negative Gay Men. Presented, American Psychological Society, August, 1988.

24. Laperrier, A., O'Hearn, P., Ironson, G., Caralis, P. Ingram, F., Perry, A., Klimas, N.G., Schneiderman, N. and Fletcher, M.A. Exercise and Immune Function in Healthy HIV Antibody Negative and Positive Gay Males. 9th Annual Society of Behavioral Medicine. Boston, MA, 1988.

25. Baron, G.A., Ashman, M.A., Fischl, M.A., Klimas, N. and Fletcher, M.A. Immunomodulation of Patients with AIDS Related Complexes (ARC) During Therapy with Recombinant Interferon Gamma (IFNG). 4th International AIDS Conf., Stockholm, June, 1988.

26. Klimas, N.G., Page, B., Chitwood, D., Ashman, M. and Fletcher, M.A. Immune Abnormalities in Street Intravenous Drug Users. 4th International AIDS Conf. Stockholm, 1988.

27. Blaney, N., Klimas, N.G., Fletcher, M.A. and Morgan, R. Mood State, Social Support and Immune Function in HIV- and HIV+ IV Drug Abusers, an AIDS Risk Group. 4th International AIDS Conf., Stockholm, June, 1988.

28. Klimas, N.G., N. Blaney, Morgan, R., Ashman, M. and Fletcher, M.A. Abnormal Lymphocyte Subsets and Natural Killer Cell Function in Anti-HIV Negative Intravenous Drug Users on Methadone. 4th International AIDS Conf., Stockholm, June, 1988.

29. Fletcher, M.A. and Klimas, N.G. Immunology Measures in Chronic Fatigue Syndrome. NIH Workshop: Design Considerations in Studies of the Chronic Fatigue Syndrome. Pittsburgh, September, 1988.

30. Klimas, N.G. The Psychoimmunology of HIV Infection in IV Drug Users. Presented at the American Psychological Association, Atlanta, 1988.

31. Millon, C., Salvato, F., van Riel, F., Blaney, N., Fletcher, M.A. and Klimas, N.G. Psychosocial Characterization of Chronic Fatigue Syndrome/Epstein-Barr Virus Patients. J. Exp. Clin. Can. Res. 7, #3, supplement:87, 1988.

32. Van Riel, F., Mantero-Atienza, E. Salvato, F., Beach, R., Fletcher, M.A., Klimas, N.G. and Fordyce-Baum, M. Nutritional Status of Chronic Fatigue Syndrome (CFS)/ Epstein-Barr Virus (EBV) Patients. J. Clin. Can. Res. 7, #3, supplement: 88, 1988.

33. Salvato, F., Fletcher, M.A., Ashman. M. and Klimas, N.G. Immune Dysfunction Among Chronic Fatigue Syndrome (CFS) Patients with Clear Evidence for Epstein-Barr Virus (EBV) Reactivation. J. Clin. Can. Res. 7, #3, supplement: 89, 1988.

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86. Lutgendorf, S. Antoni, M., Ironson, G., Starr, K., Klimas, N., Kumar. M., Cleven, K., Peneodo, F., Schneiderman, N. and Fletcher, M.A. Impact of avoidant thoughts on immune functioning in symptomatic HIV positive men.Psychosomatic Medicine Society, Boston, Ma, 1994.

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97. Klimas, N. Update on anti-retroviral therapy in HIV. SCIM, Vail Colo., 1997.

98. Klimas, N. Highly active anti-retroviral therapy: implications for adherence and immunomodulatory interventions. Academy for Behavioral Medicine Research, Cape Cod, 1998.

99. McPherson, S., Malow, R., Penedo, F.J., Jones, D., Maggio, C., Triplett, J., Klimas, N., Enhancing adherence to combination antiretroviral therapy in non-adherent HIV+ men. Presented at the annual meeting of the American Psychological Association, Boston, MA, 1999.

100. Klimas, NG - Immunology of CFS, Regional Behavioral Medicine Conference, Auckland New Zealand, Nov 2000

101. Klimas, NG, McPherson, S Adherence and Chronic Active Hepatitis C – what we have learned from HIV, 25th Intl behavioral Medicine Society Conference, Brisbane, Australia Nov 2000

102. Immunology of CFS, State of the Science Meeting, NIH Workshop, Washington DC October 2000

103 Klimas, NG , speaker: Current understanding of the Pathogenesis of CFS – NIH/CFIDS Asso Workshop on Autonomic Dysfunction and CFS, February 2001, Washington DC

104 Klimas, NG , speaker: Methodologic Issues Seminar _ NIH/CFIDS Workshop on Neuroendocrine Dysfunction and CFS, Nov 2001, Washington DC

105 Klimas, NG , speaker: Methodologic Issues in the Study of CFS – NIH/CFIDS Association Workshop on Immune Dysfunction and CFS, Feb 2002

106 Klimas, NG , speaker: Adherence to Therapy Seminar, 26th International Behavioral Medicine Society Conference, Helsinki, Finland, August 2002

107 Klimas, NG, debater participant: CFS – physical or somatic disorder? 26th International Behavioral Medicine Society Conference, Helsinki, Finland, August 2002

108 Klimas, NG , speaker : Methodologic Issues – Immunology of CFS; NIH State of the Science Meeting, Bethesda, MD, May 2003

109 Klimas NG and Turgeli, E Assessment Tools in CFS, AACFS Intl Conference Madison Wisconsin, October 2004

110 Jeffrey Greeson, Maria Llabre, Nancy Klimas, Peter Lawrence, Alex Gonzalez, Pedro Martin, Neil Schneiderman, Barry Hurwitz Psychological Distress and HIV Disease Progression: Roe of Natural Killer Cell Immunity; 2005 Annual Meeting of the American Psychosomatic Society, March 2-5, in Vancouver, Canada

111 Elevations of HHV-6 serology are associated with low NK cell Function , Nancy Klimas, Mary Ann Fletcher, Kevin Maher. International Conference on HHV6 Infection, Barcelona Spain May1-3, 2006.

112 Klimas, NG and Fletcher MA Neuropeptide Y in CFS and GWI, IACFS International Conference, Fort Lauderdale 2007

113 Vera, M, Klimas, N, Garcia L,, Fletcher MA Isoprinosine in CFS (presentation) IACFS/ME Research Conference Reno Nevada, March 2009

114 Garcia, L, Klimas N, Fletcher MA Incidence of sleep disorders in CFS sample. IACFS/ME Research Conference Reno Nevada March 2009

5c. **Funded Research (Past 5 years):**

Pending:

Cooperative studies program, Principal Proponent: Assessing genetic variables in gulf war illness, LOI accepted, protocol development funded. March 2010

"Genetic pathway Analysis in CFS" – NIH protocol submitted Mar 2010, fundable score, funding should begin in October 2010
Role: PI

Merit Review submission: Microsomal RNA role in regulatory pathway alterations of GWI. To be submitted Sept 1 2010

Funded:

"The Use of Comprehensive Molecular Profiling with Network and Control Theory to Better Understand GWI and Mode Therapeutic Strategies" Award Number W81XWH-09-2-0071,
DOD 6/2009 – 6/2011
Role: PI
R01AI065723 - 01 12/1/06 – 11/30/11
Immunologic Mechanisms, Biomarkers and Subsets in CFS
NIAID (PI MA Fletcher)
Goal of this project is to determine the immunologic basis for CFS pathogenesis
Role: Co-PI, 25% UM effort
R21AA016635-01 9/30/06-8/31/08

R21: Neuropeptide Y and dipeptidyl-peptidase IV (CD26) in chronic fatigue syndrome
NIAAA (PI MA Fletcher)
Goal of this
project to determine the relationship of neuropeptide Y and dipeptidyl-peptidase IV to natural killer cell cytotoxicity in CFS.
Role: Co-PI, 25% UM effort

Recent:

Merit Review 11/05 – 11/09
Lo**ngitudinal follow up of GWI and CFS patients**
Veterans Administration
Study of immune function and clinical symptoms in patients with Gulf War Illness.
Role: PI

Merit Review 9/06 -8/09
Gene Array Analysis of Gulf War Illness and Chronic Fatigue
Veterans Administration
Gene Array Analysis of Gulf War Illness and Chronic Fatigue Syndrome
Role: PI

Research grant 03/07 – 03/09
Mechanisms of Cytotoxic Cell Dysfunction in CFS
CFIDS (PI N Klimas)
Study of killer cells in CFS
Role: PI, 15% UM effort

R01MH066697 09/04/03-6/30/08
Psychobiological Processes and Health in HIV/AIDS
NIMH R01 (PI G. Ironson)
This grant examines psychological and biological (CTL, NK, cortisol) predictors of disease progression in HIV/AIDS.
Role: Co-I. 5% UM effort

R01 9/30/06-8/31/10
Virtual Cognitive Behavioral Therapy in Chronic Fatigue Syndrome
NIMH (PI M Antoni)
Evaluate CBT utilizing phone and web based interventions
Role: Co-I, 5% UM effort

NIH sponsored Clinical Trial 2000 - 2008
Immune Restoration with IL-2 in HIV infection – the ESPRIT study
Role: Site PI

RO1 HL72712 09/30/02-08/31/07
HIV/HCV Co-Infection: HAART and CVD Pathophysiology
NIH/NHLBI (PI Hurwitz)
HAART medication has been implicated as a potential etiopathological source of the increased prevalence of cardiovascular disease risk in HIV infected persons. The study objective is to determine whether the data collected is described by the proposed pathophysiological model.
Role: Co-I

UO1- AI- 459940 8/1/00 to 7/31/04
NIAID (PI N Klimas)
Center for Multidisciplinary studies of CFS
This was a study of the modification of the stress response through a program of cognitive behavioral stress management and its effect on immune function in patients with chronic fatigue syndrome.
Role: PI

RO1 HL65668-05 09/27/01-07/31/05
NIH/NHLBI (PI Hurwitz)
RBC Mass, ANS Integrity & Syncope Susceptibility in CFS - 1 year no cost extension
The goal of the project was to study the pathogenesis of the chronic fatigue syndrome (CFS) which includes severe and debilitating fatigue, orthostatic intolerance, and the disruption of hematological, autonomic, and cardiovascular functions.
Role: Co-PI

Celgene Corp. 2003-2005
Clinical trial of Thalidomide

Immune impact of Thalidomide in CFS
Role: PI

Dr Klimas has developed a set of outcome measures that can be utilized by multisite studies of CFS in clinical intervention or natural history trials. She is the chair of a consortium of clinicians interested in participating in clinical trials using this web-based format for assessment.

5d. **Editorial Responsibilities:**

Founding Editor: Journal of Chronic Fatigue Syndrome
Haworth Press (1992-2001)
Editorial Board, Journal of Chronic Fatigue Syndrome (2001 – current)
Ad hoc reviewer NEJM
Ad hoc Reviewer, Journal of Clinical Immunology
Ad hoc Reviewer, JAMA
Ad hoc Reviewer, Annals of Internal Medicine
Ad hoc Reviewer, AIDS
Ad hoc Reviewer, JAIDS
Ad hoc Reviewer, Psychosomatic Medicine
Ad hoc reviewer, Brain Behavior and Immunity

5e. **Professional and Honorary Organizations**:

International Association for CFS (previously AACFS), Current President
American Society for the Advancement of Science;
Association of Medical Laboratory Immunologists
Clinical Immunology Society
Association of Women in Science;
American Medical Woman's Association
University of Miami Medical Women
Miami Medical Women's Association (VP)

5f. **Honors**:

2004 – Honorary Degree, University of Catalonia, Barcelona Spain.
1998 - Fellow - Academy for Behavioral Medicine Research
1992 - Iron Arrow (University of Miami Honor Association)
1982 - Finalist Beecham Award, Southern Blood Club
1982 - Finalist Burroughs-Wellcome Young Investigator Award
1983 - Southern Medical Association Research Award
1984 - National Research Service Award
1985 - American Cancer Society Institutional Research Award

5g. **Other Professional Activities**:

Miami VAMC AIDS Clinical and Research Unit Developed and wrote the proposal for the Miami VAMC AIDS Clinical and Research Unit, which was one of 3 selected for funding. The proposal included 3 million dollars in construction funds as well as infrastructure support. This resulted in one of the top VA HIV/AIDS clinical and research programs in the US, which is still in operation. Dr Klimas is Director of AIDS Research and Co-director of the Clinical HIV/AIDS program at the Miami VAMC. 1987 to present

University of Miami and VAMC CFS and GWI Research Center : Initially funded with an NIH center grant, ans since supported with NIH , VA, DOD, and private foundation grants, the center is a clinical , translational, and basic science center that integrates research across disciplines. Current studies include genomics, immune, neuroendocrine studies , a anural history study, and clinical trials. Dr. Klimas is Center PI and coordinates the research efforts of four research groups.

Canadian Government advisor in the development of the Clinical Case Definition for Chronic Fatigue Syndrome/Myalgic Encephalitis 2001, which is being revised in 2008.

Whittemore Peterson Institute - This University of Nevada institute is located in Reno, and is in its start up years, developing a clinical research program and a comprehensive clinic for patients with CFS/ME. Dr klimas has been advising its executive committee on long term research goals. The institute is constructing a 25 million dollar facility which should open its doors in 2010.

6 month sabbatical CDC 2001 –, Molecular Epidemiology Program Viral Exanthems and Herpesvirus Branch, Developed the international protocol currently underway to define empirically CFS.

IACFS/ME
Dr. Klimas served as President of the International Association for Chronic Fatigue Syndrome (A national professional organization of investigators and clinicians) from 2005-2007 and was re-elected for another 3-year term in January of 2007. She organized the IACFS conference in Fort Lauderdale in January, 2007, and the conference in Reno Nevaa in March 2009. Each of these conferences were attended by 400 patients and 350 professionals, and provided a unique opportunity for patients to meet and talk with leading international researchers and clinicians.

CFSAC: Chronic Fatigue Syndrome Advisory Committee
In 1996, Secretary for Health Donna Shalala chartered a special committee to advise the Department of Health and Human Services (DHHS) on policy regarding chronic fatigue syndrome (CFS), also known as chronic fatigue and immune dysfunction syndrome or CFIDS or Myalgic Encepahalomyelopathy (ME). This committee, known as the DHHS Chronic Fatigue Syndrome Coordinating Committee (CFSCC), brought together officials representing various health agencies together with seven appointed members of the public to improve coordination of federal CFS programs. A year 2000 review of federal activities on CFS conducted by the General Accounting Office prompted several changes. Among them was the replacement of the CFSCC with a new committee, the CFS Advisory Committee (CFSAC), whose structure more closely matched other DHHS advisory bodies. Secretary Michael Leavitt most recently renewed the charter on August 30, 2006. Nancy.Klimas served on this committee from 1997 to 2000. She was reappointed to another three-year term on the committee in 2007, which has been extended to 2011.

National Press Club in Washington, DC: The CDC's Chronic Fatigue Syndrome Public Education and Awareness Campaign.

Nancy Klimas was a participant at this event held on November 3, 2006. Present were Julie Gerberding, CDC, John Agwunobi, HHS, William Reeves, CDC and Anthony Komoroff, Harvard. Dozens of reporters from national and local media outlets across the United States were in attendance, and many others participated via phone link. Dr. Klimas remarked, "Historically, the lack of credibility afforded this illness has been a key obstacle to understanding it. Today, with solid evidence that CFS has identifiable biologic underpinnings, and with evidence that people with CFS experience a level of disability equal to that of patients with multiple sclerosis, advanced HIV disease and undergoing chemotherapy, I hope we can begin to put an end to the stigma surrounding this illness." Dr. Klimas also focused on treatments, saying, "Although there's no single treatment—no hoped for 'magic bullet'—that fixes the illness at its core, there are treatments that can improve symptoms, increase function and allow CFS patients to engage in activities of daily living. Current best practices for clinical care include a combination of symptom management, activity management and exercise therapies."

Chronic Fatigue Centers for Research and Clinical Care: A newly conceived program hoping to use clinical care templates to help diagnose and manage complex CFS/ME cases while collecting research data and developing the patient base for clinical trials work. Dr. Klimas is the senior clinician developing the templates the first clinic to implement this format is the Chronic Fatigue Center in Kendall, FL which opened in 2010.

5h. **Consultantships**

1987 - 1990 - VA National AIDS Steering Committee

1987 - 1990 - VA National AIDS Research Subcommittee

1987 - 1991 - VA Train the Trainer National AIDS Education Program

1988 - Present - VA National AIDS Prevention and Counseling Training Program

1988 - Present - Special Review Committee, National VA AIDS Prevention and Education

1990 – 2000 - VA National HIV Therapeutics Advisory Committee

1991 - 2000 - Board of Directors, American Association for Chronic Fatigue Syndrome (An international professional organization of investigators and clinicians).

2002 – present - Board of Directors, American Association for Chronic Fatigue Syndrome (An international professional organization of investigators and clinicians).

1992 - Chairperson of the Program Committee for the First International Meeting: Chronic Fatigue Syndrome, held in Albany NY, sponsored by the AACFS, NIH and CDC.

1994 - Local Coordinator and Program Committee member for the Second International Meeting: Chronic Fatigue Syndrome research Conference, held in Ft Lauderdale, October 1994, sponsored by AACFS, NIH, CDC, and Univ. of Miami.

1994 - Chairperson of the Program Committee for the CFS Clinical Conference, held in Ft. Lauderdale, October 1994, sponsored by AACFS.

1991- 1997 Consultant to Center for Special Immunology, Inc., Ft. Lauderdale, FL.

1993 - 2000 - Board of Directors, American Association for Chronic Fatigue Syndrome.

1993- Present Medical Advisory Board, Chronic Fatigue and Immunodeficiency Syndrome Foundation.

1993- 1998 - Medical Advisory Board, Environmental Health Foundation.

2000 NIH State of the Science CFS Conference planning committee

2001 – present Name Change subcommittee, HHS CFS coordinating Committee

1999-present – CDC CFS Case Definition Revision Committee

2001 Canadian CFS Clinical Case definition expert panel

2001 CDC Expert Advisory Panel – long term outcomes study

2002 – present NIH reviewer and site visitor GCRC applications

2001- present Ad Hoc reviewer, Medical Research Council, United Kingdom.

2003 –present NIH reviewer CFS Special Emphasis Panel

2003 Brighton Collaboration on CFS Case Definition

2003 Elected to the Board of Directors, AACFS, 7 year term

2005 - 2009 President of the International Association for Chronic Fatigue Syndrome – this international organization of investigators and clinicians sponsors international and regional meetings, has developed a peer review journal, and works with government and regional groups to develop curricula and provider education programs.

2007 – 2011 CFSAC HHS Advisory committee to the Secretary of Health and Human Services

2010 – current Principal Proponent, National Gulf War Illness genomic bank and GWAS study, a VA cooperative study approved for planning, full protocol to be reviewed in Fall 2010.

5i. **TEACHING**

Teaching Award:

Woman Faculty Member of the Year, 1989, UM Medical Women.

Current Teaching Responsibilities:

Housestaff, Graduate Program, Medical School and Undergraduate lecturer (see lectures listed above)

General topics:
Clinical Immunology, Medical Laboratory Immunology, HIV Infection, Health and Human Values: Psychoneuroimmunology, Allergy and Immunology, CFS, Gulf War Illness, Stress and Disease.

Internal Medicine, Ward Attending, VA Medical Center (3 months/ year)

Allergy Clinic rotations for medical students, housestaff and Harrington Latin American Scholars.

HIV and Immunology rotations for medical students, housestaff and Harrington Latin American Scholars

Nationally/Internationally helped to develop CME course work for clinicians in the diagnosis and treatment of CFS in collaboration with the CDC and CFIDS Association of America

Dissertation Advising:

Masters and Doctoral Students in Psychology (9 PhD candidates/3 MS candidates over last 5 years)

6. SERVICE TO THE UNIVERSITY

6a. University Committees:

1. Medical School Admissions Committee, 1984-1987.
2. VA Human Subjects IRB, 1987.
3. Faculty Sponsor, UM Medical Women, 1985 - Present.
4. UMHC Infection Control Committee, 1989 - 1992.
5. VAMC Research Space Committee, 1988 - 1989.
6. VA Research and Education Foundation Board of Directors – 1999- present
7. Search Committee - AIDS/HIV senior and junior research faculty
8. Selection Committee – applicants for AAMC Women in Medicine Leadership Program
9. Executive Committee, GCRC 2002 – present
10. Executive Committee, Behavioral Medicine Research Center, 1999 - present
11. University of Miami Committee on Rank Salary and Conditions of employment 2003-2004
12. VA Research Committee, alternate 2004-present
13. Faculty Senate Professional Conduct Panel 2003 – present
14. University of Miami Miller School of Medicine Self Study LCME Women and Minority subcommittee 2007- present

6b. Clinical Responsibilites

1. Co-director of VA Medical Center AIDS Clinical Unit,
2. HIV/AIDS Primary Care Clinic (Silver Team) – attending Monday clinic, and backing up Wednesday clinic. Daily oversight of 2 ARNP clinics.
2. General Medicine teaching attending, VAMC
3. Director, Miami VAMC Allergy Clinic, Tuesday MD clinic, and oversight of Wednesday RN clinic
4. Director of Allergy and Diagnostic Immunology outpatient clinic, University of Miami, Thursday Clinic
5. Director, CFS and GWI Clinical and Research Center, University of Miami and Miami VAMC

Consistently ranked “Outstanding” in the annual VAMC proficiency reporting, including clinical skills, teaching, productivity and administration.

7. COMMUNITY ACTIVITIES

Health Crisis Network, Co-Founder and Past Chair of the Medical Advisory Committee and Board of Directors. (Currently Co-Cure Foundation, a Miami Dade HIV related community health organization) 1984, 1985-89

Member, National Task Force on Women's Health Issues, National Organization for Women.(1995-present)

People with AIDS Coalition (PWAC), Board of Directors 1993-95

PWA Housing Coalition, Board of Directors 1993-95

Women's Emergency Network, Board of Directors 1998/99

Bessie Garrett Foundation – Homeless children outreach, Board of Directors 1999 – present

National Organization for Women, Women's Health Advisory Board, 1992-2002

PANDORA – advocacy for people with neuroinflammatory disorders, board of directors

APPENDIX G: Gordon Broderick, Ph.D. Curriculum Vitae

CONTACT INFORMATION

Home.

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Ph. 780-445-4666 Fx. 780-407-6384 Email. gordon.broderick@ualberta.ca

Citizenship: Canadian Languages: French and English both spoken and written fluently

EDUCATION AND TRAINING

Ph.D. Chemical Engineering	École Polytechnique de Montréal	1991-1994
Masters Chemical Engineering	McGill University	1988-1989
Bachelor Mechanical Engineering	McGill University	1980-1984

LICENSES.

Ing. (P. Eng.)	Ordre des Ingénieurs du Québec	1986-present

HONORS AND AWARDS

Nightingale Award for Community Service, ME Society of Edmonton	2010
Associate Editor BMC Systems Biology 2010	
Invited member US Veteran's Administration Committee on Gulf War Illness	2010
Teacher of the Year Award (Small Group Case Study)	2008
Dean of Graduate Studies and Research Award for best doctoral thesis.	1994
Natural Sciences and Engineering Research Council of Canada Award (Ph.D)	1991 - 1994
John S. Bates Centennial Fellowship (Ph.D)	1992 - 1993
R.M. Fowler Memorial Fellowship (Masters)	1988 - 1989
Natural Sciences and Engineering Research Council of Canada Award (Masters)	1988 - 1989
J.B. Lynch Foundation Award (Bachelor)	1980 - 1984

PROFESSIONAL /ACADEMIC POSITIONS HELD

Associate Professor – Dept. of Medicine, July 1, 2006 – Present
Faculty of Medicine and Dentistry, University of Alberta • Edmonton, AB
Reporting to the Department Chair, establish independent research program in the area of computational medicine.
Major Contributions: (1) Principal investigator in computational research effort directed at understanding immune cell activation and population kinetics in chronic inflammatory illnesses (2) Actively developing agent-based model of the spatial dynamics of immune cell migration and signalling in the context of neuro-immune dysfunction. (3) Co-investigator /computational group leader in $12M project directed at understanding gene regulatory mechanisms involved in injury and alloimmune response of kidney grafts.

Project Leader – Cell Simulation 2002 – 2006
Institute for Biomolecular Design – University of Alberta • Edmonton, AB

Reporting to the Executive Director, direct the research activities of an interdisciplinary group of 4-6 programmers and engineers working to create spatially discrete mathematical models of cell life. **Major Contributions**: (1) Lead architect in creation of scalable agent-based high-performance computational framework for whole cell simulation, (2) Developed scientific strategy behind $9.5M IBM sponsorship of dedicated high-performance computing platform, (3)Developed first agent-based model of cell membrane chemistry / mechanics, (4) 2 U.S. Provisional Patents, 2 PCTs in 18 months.

Consulting Biostatistician – Transplant Transcriptome Project **2004 – 2005**
Alberta Transplant Applied Genomics Centre – University of Alberta • Edmonton, AB
Reporting to the Executive Director, assist in the development of a strategy for ensuring the use of leading edge data analysis tools in supporting the research activities. **Major Contributions**: (1) Outlined standardised data handling and analysis pipeline, (2) Designed multivariate calibration filter for reconciliation of new micro-array architecture with previous generation, (3) Proposed strategy for establishing future biostatistics team, identifying key internal and external contributors.

Principal Scientist **1999 – 2002**
Noranda Technology Center • Pointe-Claire, QC
Reporting to the Senior Vice-President Technology, formulate company-wide plan for developing strategic technologies in advanced process systems. Direct research efforts of project leaders in this area. Principal investigator with substantial discretion, define and execute high-impact research. **Major Contributions**: (1) Developed novel Monte Carlo signal processing technique for estimating particle size distributions from laser pulse patterns, (2) Lead research collaboration with McGill University directed at modelling complex spatial distributions using discrete stochastic automata, (3) Lead high-risk collaboration with University of Lund aimed at innovative applications of artificial reasoning (reinforcement learning) for advanced diagnostics.

Visiting Scientist **2000 – 2001**
McGill School of Computer Science / Montreal General Hospital • Montreal, QC.
Responsible for computational aspects of multidisciplinary effort directed at elucidating pathway kinetics and specificity of steroid-containing drugs in treating immune disorders using gene expression time course sequences. **Major Contributions**: (1) Completed n-way projection analysis of multi-tissue time-course responses to steroid impulse stimuli, (2) Implemented and evaluated algorithm for multivariate linear filtering, discovery and class prediction for AML and ALL-type leukemia, (3) Conducted comparison of results from PCA and self-organising maps (SOM) for extraction of features from gene expression in yeast cell cycle data.

Senior Scientist **1995 – 1999**
Noranda Technology Center • Pointe-Claire, QC
Initiate and actively lead new research projects using discretionary funding to identify promising new technologies, develop proof of concept. Effectively coordinate academic and private consultants. Appointed by Senior Vice-President Technology to committee reviewing Noranda's high-impact research initiatives. **Major Contributions**: (1) Patented innovative energy-saving refining strategy. (2) Established partnership with Colorado State University, and Hong Kong University in evolutionary programming. (3) Established research partnership with University of Waterloo for wavelet-based adaptive estimation and control. (4) Defined, and obtained funding for a 2-year collaborative research with McGill University on cellular automata (CA).

Research Engineer/Project Leader **1989 - 1995**
Noranda Technology Center • Pointe-Claire, QC
Optimize process performance by applying mathematical modeling and simulation techniques. Develop and maintain close ties with academic institutions and other private research facilities to help identify promising new technologies, transfer, and adapt these to meet strategic needs. Act as a technical leader in statistical process modeling. **Major Contributions**: (1) Developed detailed product quality models based on intrinsic material properties. (2) Constructed novel multivariate statistical approach to quality monitoring. (3) Successfully implemented PLS model-based system for on-line prediction and quality optimization.

RESEARCH

Invited presentations.

Broderick, G. 2010. Networked Regulatory Systems in Complex Illness. Developmental Center for AIDS Research. University of Miami, Miami, FL, February 16.

Broderick, G. 2010. A Systems Biology Approach to Understanding Homeostasis Reset - the CFS/GWI Experience. John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL, February 16.

Broderick G. 2009. Subtle Immune Signatures in Chronic Fatigue Syndrome and Gulf War Illness. From Infection to Neurometabolism: A Nexus for CFS. The Banbury Centre, Cold Spring Harbor Laboratory, Long Island, NY, Sept. 13-16, Closed session.

Broderick G, Klimas N, 2009. Immune Network Dysfunction in Gulf War Illness. Research Advisory Committee, U.S. Department of Veterans Affairs, Boston, MA, June 29-30.

Broderick G. 2009. Discovery Learning: A Preceptor's Impressions. Academic Half-day, Geriatric Division, Glenrose Rehabilitation Hospital, Edmonton, AB, June 16.

Broderick G, 2009. CFS/ME Lifting the Veil on a Complex Illness. Guest Speaker, M.E. Awareness Day, M.E. Society of Edmonton, Edmonton, AB, May 11.

Broderick G, 2009, Chronic Fatiguing Illnesses: Immune Signatures and Beyond. Research Roundtable Guest Speaker. The CFIDS Association of America, Chicago, IL, May 3.

Broderick G, Fletcher MA, Vernon SD, Klimas N, 2009, Isolating Characteristic Immune Signals under Challenge in Gulf War Illness. Int Assoc CFS/ME, Reno, NV, March 12-15.

Klimas N, Fletcher MA, Broderick G, 2008, Gulf War Syndrome: A Systems Biology Approach. Keynote address, Acad. Behavioral Medicine Ann. Meeting, Lake Louise, AB, June 14-16.

Vernon SD, Fuite J, Broderick G. 2008. Genetic Variation and Altered Immune Activity in Chronic Fatigue Syndrome. 6th Int Conf HHV-6 Foundation, Int Symp on Viruses in Chronic Fatigue Syndrome and Post-viral fatigue, Baltimore, MD, June 22-23.

Broderick G, Schaefer CF, Einecke G, Halloran PF, 2008, Identifying Changes in Gene Regulatory Motifs in Rejection of Human Kidney Transplants, Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada, Jan. 25.

Vernon SD, Fuite J, Broderick G. 2008. Neuroendocrine and Immune Network Re-modeling in Chronic Fatigue Syndrome. Integrative Neural Immune Interest Group (INIIG) Lecture Series, National Institute of Mental Health, Bethesda, MD, March 4.

Broderick G. 2008. Agent-based Models in Medicine: the Promise and the Challenges. Invited keynote speaker. SwarmFest 2008, Northwestern University Feinberg School of Medicine, Chicago IL, May 12-13.

Broderick G, Ben-Zvi A, Aslakson E, Klimas N, Vernon SD. 2007. An MPC-guided Approach for the Regulation of Cortisol in a Hypothalamic-pituitary-adrenal Axis Model. Invited talk, Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, Aug. 29.

Broderick G, Bolshin C, Aspler AL. 2007. Evidence of Lymphcyte Imbalance in Wichita Study of CFS sufferers. Centers for Disease Control and Prevention (CDC), Atlanta, GA, August 27.

Broderick, G, 2007. Delayering the Data: Revealing Rejection in Human Kidney Transplants by isolating Gene Set Co-expression. Invited talk, Using the "Omic" technologies to Phenotype Disease: A Satellite Symposium of the 9th Banff Conference on Allograft Pathology. Edmonton, AB, June 18-19.

Broderick G, 2006. Composite Features of Fatigue. Invited Speaker, Computational Challenge (Team 2), Centers for Disease Control and Prevention (CDC), Atlanta, GA, March 15.

Broderick G, 2006, The Virtual Cytoplasm: Exploring Complex Intra-cellular Kinetics. Department of Mathematical & Statistical Sciences, University of Alberta, Edmonton, Alberta, Canada, Feb. 27.

Broderick G, 2005. CFS: From Constructs to Mechanisms", Invited Speaker, CDC Computational Challenge (Team 2), Banbury Centre Workshop, From Markers to Models: Integrating Data to Make Sense of Biologic Systems, Cold Spring Harbor Laboratory, Long Island, N.Y., Sept. 18-21, Closed session.

Broderick G, 2005. The Virtual Cell Model: Exploring Emergent Behaviour in Nature's Inherent Integration Milieu, Invited Speaker, Realistic Modelling of Biological Systems: A First International Workshop, Weizmann Inst. of Science, Rehovot, Israel, May 2-4.

Broderick G, 2005. Integrating a Model Biological Membrane and Virtual Cytoplasm. Invited Speaker, Realistic Modelling of Biological Systems: A First International Workshop, Weizmann Inst. of Science, Rehovot, Israel, May 2-4.

Broderick G, 2005. Building a Large-scale Functional Model of a Biological Membrane. Invited Speaker, Faculty Talk, Center for Complexity Science, Weizmann Inst. of Science, Rehovot, Israel, May 1.

Broderick G, 2004. A Parallel Particle-based Approach to Whole-cell Modelling. Invited Speaker, Banbury Centre Conference on Integrating Disparate Data to Simulate Lymphocyte Function, Cold Spring Harbor Laboratory, Long Island, N.Y., Sept. 19-22, Closed session.

Broderick G, Ru'aini M, Winters P, Chan E, Ellison MJ, 2004. Towards a Life-like Virtual Cell Using Discrete Automata. Departmental Seminars in Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta, Canada, December 2.

Grant support.

Awarded

U.S. Department of Defense **July 2009 – June 2011**
The Use of Comprehensive Molecular Profiling with Network and Control Theory to Better Understand GWI and Model Therapeutic Strategies
Budget (Co-investigator U of A): $162,000 ($130,000 USD)

CFIDS Association of America **March 2009 (1.5 year term)**
Molecular Patterns of Persistent Immune Activation in a Post-infectious Adolescent Cohort
Principal Investigator,
Budget (PI): $156,000 ($125,000 USD).

Alberta Heritage Foundation for Medical Research **May 2009 – April 2014**
Title of team program: Etiology of Inflammatory Bowel Disease: Gene, Microbe, and Environment Interactions
Budget (Co-investigator U of A): $350,000

University of Alberta, Faculty of Medicine and Dentistry **July 2009 - August 2009**
Henry Anton Deutsch Medical Summer Research Award (in support of summer student research)
Budget: $2,400

University of Alberta, Faculty of Medicine and Dentistry **July 2009 - August 2013**
Title of Program: Biomarkers for Gulf War Illness (Research Award in Support of Summer Studentships in Broderick Laboratory)
Budget: $3,500

NIH
A Prospective Study of CFS in Adolescents **January 2008 – January 2010**
Co-investigator; Principal Investigator: Dr. R. Taylor, University of Illinois in Chicago
Budget (Co-investigator U of A): $ 5,000/year for 2 years

Pending

National Institutes of Health (NIH) **July. 2010 – June. 2014**
Information Thermodynamics of Immune Networks in Chronic Inflammation, Fatigue and Cancer. R01 Eureka Program.

Budget (PI): $845,000 ($796,000 USD)

U.S. Department of Defense **July 2010 – June 2012**
Autoantibody profiling to identify predisposing auto-reactivity to myalgia-arthralgia-fatigue syndromes.
Budget (Co-investigator U of A): $225,000 ($180,000 USD)

U.S. Department of Defense **July 2010 – June 2013**
Theory-driven Models for Correcting "Fight or Flight" Imbalance in Gulf War Illness.
Budget (PI): $728,000 ($679,000 USD)

National Institutes of Health (NIH) **Dec. 2009 – Nov. 2014**
Study of Chronic Fatigue Syndrome using comprehensive molecular profiling with network and control theory. R01.
Budget (Co-investigator U of A): $375,000 ($300,000 USD)

Administrative supplement: Study of Chronic Fatigue Syndrome using comprehensive molecular profiling with network and control theory.
Budget (Co-investigator U of A): $38,000 ($30,000 USD)

U.S. Department of Veterans Affairs **Oct. 2009 – Sept. 2012**
Placebo controlled phase II double blind randomized clinical trial of inosine pranobex in GWI and CFS.
Budget (Co-investigator U of A): $64,000 ($60,000 USD)

Previously held
University of Alberta, Faculty of Medicine and Dentistry **July 1, 2006 - June 30, 2009**
Start-up Grant N031000099: Mechanistic analysis of microarray signatures in transplant rejection. Budget $60,000.

Genome Canada **July 2006 – December 2007**
Transplant Transcriptome Project
Co-investigator; Principal Investigator: Dr. P.F. Halloran, University of Alberta
Budget (Co-investigator U of A): $ 60,000/year for 1.5 years

NSERC
Real-time adaptive pattern recognition using cellular automata **July 1997 – July 1999**
Industry co-investigator; Principal Investigator: Dr. D. Thérien, McGill University
Collaborative Research and Development (CRD)
Budget: $280,000 over 2 years

Optimisation of high-yield sulphite pulping **May 1990 – April 1994**
Industry co-investigator; Principal Investigator: Dr. J.L. Valade, Dr. J. Paris, École Polytechnique de Montréal
Collaborative Research and Development (CRD)
Budget: $140,000 over 4 years

Reviewing activities.
Review of candidates for faculty positions.
2008. Candidate Senior Lecturer; Faculty of Life Sciences; University of Bar-Ilan, Israel
2006. Candidate Senior Lecturer; Dept. of Bio-medical Eng., Ben Gurion University, Israel

Grant reviews
2010 Health Research Awards, the Health Research Board (HRB) of Ireland, Dublin, Ireland
Chief Scientist Office of the Scottish Government Health Directorate, Edinburgh, UK
2009 U.S.-Israel Bi-national Science Foundation, Jerusalem, Israel
Chief Scientist Office of the Scottish Government Health Directorate, Edinburgh, UK (2 grant proposals)
Microsoft Research PhD Scholarship Programme. Microsoft Research, Cambridge, UK (2 proposals)
Canadian Institutes of Health Research (CIHR)

Natural Sciences and Engineering Research Council of Canada (NSERC)
2006. The Centre for Complexity Science, Jerusalem, Israel

Peer review of publications.
2010. Associate Editor, BMC Systems Biology, BioMed Central, London, UK (Impact 3.71)
2009. Journal of Immunology
Journal of Infectious Diseases
BMC Medical Genomics
American Journal of Transplantation
Cellular and Molecular Life Sciences
Brain, Behavior, and Immunity (2 manuscripts)
2008. Molecular Medicine
The Journal of Physical Chemistry
American Journal of Transplantation (2 manuscripts)
PLoS One
2007. Transplantation (with Dr. Bruce Kaplan, University of Illinois in Chicago).
Bioinformatics; Oxford Press (2 manuscripts).
American Journal of Transplantation (2 manuscripts)
BMC Neurology
Theoretical Biology and Medical Modeling
2006. PLoS Computational Biology
2002 and previous
Canadian Journal of Chemical Engineering (regularly requested)

Peer review of conference abstracts
2009 Department of Medicine Research Day Graduate Student Poster Session (6 posters)

Bibliography.

Refereed journals.

Fletcher MA, Rosenthal M, Antoni M, Ironson G, Zeng X-R, Harvey J, Barnes Z, Hurwitz B, Levis S, Broderick G, Klimas NG. Neuropeptide Y: a marker for stress and symptom severity in chronic fatigue syndrome. In preparation.

Broderick G, Andrea Kreitz, Fuite J, Fletcher MA, Vernon SD, Klimas NG. Remodeling of Lymphocyte-cytokine Networks in Gulf War Illness under Challenge. Brain Behav Imm. 2010; Under review.

Broderick G, Fletcher MA, Gallagher M, Vernon SD, Klimas NG. Characteristic Immune Response to Exercise Challenge in Gulf War Illness. BMC Clin Pathol. 2009; Under review.

Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. Circadian rhythms in cytokine secretion in chronic fatigue syndrome. Brain Behav Immun. 2010 Jun 19.

Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. Formal Analysis of Cytokine Networks in Chronic Fatigue Syndrome. Brain Behav Immun. May 4, 2010. [Epub ahead of print].

Fletcher MA, Zeng XR, Maher K, Levis S, Barry H, Antoni M, Broderick G, Klimas NG. Biomarkers in chronic fatigue syndrome: Evaluation of natural killer cell function and dipeptyl peptidase IV. PLoS ONE. 25 May, 2010 | 10.1371/journal.pone.0010817.

Nakamura T, Schwander SK, Donnelly R, Ortega F, Togo F, Broderick G, Yamamoto Y, Cherniack NS, Rapoport D, Natelson BH. Cytokines across the night in chronic fatigue syndrome with and without Fibromyalgia. Clin Vaccine Immunol. 2010 Feb 24. [Epub ahead of print]

Ben-Zvi A, Vernon SD, Broderick G. 2008. Model-based Therapeutic Correction of Hypothalamic Pituitary Adrenal Axis Dysfunction. PLoS Comput Biol 5(1): e1000273. doi:10.1371/journal.pcbi.1000273.

Aspler AL, Bolshin C, Vernon SD, Broderick G. 2008. Evidence of Inflammatory Immune Signaling in Chronic Fatigue Syndrome: A Pilot Study of Gene Expression in Peripheral Blood. Behav Brain Funct Sep 26;4(1):44. doi:10.1186/1744-9081-4-44.

Fuite J,Vernon SD, Broderick G. 2008. Neuroendocrine and Immune Network Re-modeling in Chronic Fatigue Syndrome: An Exploratory Analysis. invited submission, Genomics 92(6): 393-399. doi:10.1016/j.ygeno.2008.08.008 (issue cover).

Zhao J, Ridgway D, Broderick G, Kovalenko A, Ellison M, 2008. Extraction of elementary rate constants from global network analysis of E. coli central metabolism. BMC Systems Biology 2:41doi:10.1186/1752-0509-2-41.

Ridgway D, Broderick G, Ru'aini M, Winter P, Lopez-Campistrous A, Ellison MJ. 2008. Coarse-grained molecular simulation of diffusion and reaction kinetics in a crowded virtual cytoplasm. Biophys J May 15;94(10):3748-59.

Mueller TF, Einecke G, Reeve J, Sis B, Mengel M, Jhangri G, Bunnag S, Cruz, J, Wishart D, Meng C, Broderick G, Kaplan B, Halloran PF, 2007. Microarray analysis of rejection in human kidney transplants using pathogenesis-based transcripts sets. Am J Transplant 7(12): 2712-2722.

Famulski KS, Broderick G, Einecke G, Hayl K, Cruz J, Sis B, Mengel M Halloran PF. 2007. Transcriptome analysis reveals heterogeneity in the injury response of kidney transplants. Am J Transplant 7: 1–13.

Einecke G, Broderick G, Sis B, Halloran PF, 2007. Early loss of renal transcripts in kidney allografts: relationship to morphologic changes and alloimmune effector mechanisms. Am J Transplant, 7(5): 1121–1130.

Broderick G, Rubin E, 2006. The Realistic Modelling of Biological Systems: A Workshop Synopsis. ComPlexUs 3:217–230.

Ridgway D, Broderick G, Ellison MJ, 2006. Accommodating space, time and randomness in network simulation. Invited paper. Curr Opin Biotechnol 17:1-6.

Broderick G, Craddock RC, Whistler T, Taylor R, Klimas N, Unger ER, 2006. Identifying illness parameters in fatigue syndromes using classical projection methods. Pharmacogenomics 7 (3): 407-419.

Whistler T, Craddock RC, Taylor R, Broderick G, Klimas N, Unger ER, 2006. Gene expression correlates of fatigue. Pharmacogenomics 7(3): 395-405.

Craddock RC, Taylor R, Broderick G, Whistler T, Klimas N, Unger ER, 2006. Exploration of statistical dependence between illness parameters using the Entropy Correlation Coefficient. Pharmacogenomics 7(3): 421-428.

Lopez-Campistrous A, Semchuk P, Burke L, Palmer-Stone T, Brokx SJ, Broderick G, Bottorff D, Weiner JH, Ellison MJ, 2005. Localization, Annotation & Comparison of the Escherichia coli K-12 Proteome under Two States of Growth, Mol. Cell. Proteomics, May 19; 10.1074/mcp.D500006-MCP200.

Broderick G, Ru'aini M, Chan E, Ellison MJ, 2004. A Life-like Virtual Cell Membrane Using Discrete Automata. Invited Paper, In Silico Biology 5: 0016.

Fenton TE, Budman HM, Pritzker MD, Bernard E, Broderick G, 2003. Modeling and Simulation of Oriented Strandboard Pressing. Ind. Eng. Chem. Res. 42(21): 5229 – 5238.

Tessier P, Broderick G, Plouffe P, 2002. Competitive Analysis of North-American Newsprint Producers Using Composite Statistical Indicators of Product and Process Performance. Pulp & Paper Canada 103(5): T140-143.

Knapp T, Budman H, Broderick G, 2001. Adaptive Control of a CSTR with a Neural Network Model. Journal of Process Control, 11: 53-68.

Tessier P, Broderick G, Plouffe P, 2001. Competitive Analysis of North-American Newsprint Producers Using Composite Statistical Indicators of Product and Process Performance. Tappi Journal 84(3): 81.

Tessier P, Broderick G, Desrochers C, 2000. Chip Size Distribution for an Ultra-high-yield Sulfite Process. Tappi Journal 83(4): 76.

Broderick G, Handle B, Paschen P, 1999. Strategies for Optimal Operation of the Tellurium Electrowinning Process. Metallurgical and Materials Transactions B, 30B(1): 5-13.

Broderick G, Cacchione E, Heroux Y, 1998. The Importance of Distribution Statistics in the Characterisation of Chip Quality. Tappi Journal, 81(2): 131-142.

Tessier P, Broderick G, 1997. Industrial Implementation of Motor Load and Freeness Control of Chemimechanical Pulp Refiners. Tappi Journal, 80(12): 135-142.

Handle B, Broderick G, Paschen P, 1997. A Statistical Response Surface Study of the Tellurium Electrowinning Process. Hydrometallurgy, (46): 105-120.

Broderick G, Lanouette R, Valade JL, 1997. Optimizing Refiner Operation with Statistical Modelling. Canadian Journal of Chemical Engineering, 75(1): 79-87.

Broderick G, Paris J, Valade JL, 1996. Fibre Development in Chemimechanical Pulp Refining, Tappi Journal, 79(4): 193-201.

Broderick G, Paris J, Valade JL, 1996. The Impact of High-yield Pulping Pretreatment Conditions on Spent Liquor Toxicity and Oxygen Demand. Paperi ja Puu, 78(1-2): 43-50.

Broderick G, Paris J, Valade JL, Wood J, 1996. Linking the Fibre Characteristics and Handsheet Properties of a High-Yield Pulp. Tappi Journal, 79(1): 161- 169.

Broderick G, Paris J, Valade JL, 1995. Factors Affecting the Optimal Performance of a High-Yield Pulping Operation. Canadian Journal of Chemical Engineering, 73(3): 391-399.

Broderick G, Paris J, Valade JL, Wood J, 1995. Applying Latent Vector Analysis to Pulp Characterization. Paperi ja Puu 77(6-7): 410-418.

Broderick G, Paris, J, Valade JL, 1995. A Composite Representation of Pulp Quality. Chemometrics and Intelligent Laboratory Systems 29(1): 19-28.

Broderick G, Valade JL, Paris J, 1993. High Yield Sulphite Pulping Based on a Plackett-Burman Design. Pulp and Paper Canada 94(9): T248-251.

Abstracts

Katz B, Fletcher MA, Taylor R, Vernon SD, Broderick G. 2010. Cytokine Expression as a Potential Prognostic Indicator in Post-infectious Fatigue. Joint Meeting of the International Cytokine Society (ICS) and the International Society for Interferon and Cytokine Research (ISICR), Chicago, IL, Oct. 3-7.

Yang C, Vernon SD, Broderick G. 2009. Cognitive Performance in a Population-based Cohort of CFS Patients. Poster presentation. 95th Annual Clinical Congress, American College of Surgeons, Chicago, IL, Oct. 11-15.

Yang C, Vernon SD, Broderick G. 2009. Cognitive Performance in a Population-based Cohort of CFS Patients. Poster presentation. 42nd Annual Summer Students Research Day, Faculty of Medicine and Dentistry, University of Alberta, Oct. 17: poster 154.

Broderick G, Fletcher MA, Vernon SD, Klimas N, 2009, Isolating Characteristic Immune Signals under Challenge in Gulf War Illness. Int Assoc CFS/ME, Reno, NV, March 12-15: Oral session Abstracts/ Latest Research in Immunology, abstract #3.

Broderick G, Fuite J, Fletcher MA,Vernon SD, Klimas N, 2009, Remodeling of Lymphocyte-cytokine networks in Gulf War Illness under Challenge. Int Assoc CFS/ME, Reno, NV, March 12-15: Poster Abstracts/ Latest Research in Immunology, poster abstract #1.

Fuite J, Vernon SD, Broderick G. 2008, Re-modelling of neuroendocrine-immune interaction in Chronic Fatigue Syndrome. Department of Medicine Research Day, University of Alberta, Edmonton AB, May 29: Abstract 67.

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Broderick G, 2005. The Virtual Cell Model: Exploring Emergent Behaviour in Nature's Inherent Integration Milieu. Invited Speaker, Realistic Modelling of Biological Systems: A First International Workshop, Weizmann Inst. of Science, Rehovot, Israel, May 2-4.

Broderick G, 2005. Building a Large-scale Functional Model of a Biological Membrane. Invited Speaker, Faculty Talk, Weizmann Inst. of Science, Rehovot, Israel, May 1.

Broderick G, Ru'aini, Ellison MJ, 2004. A Parallel Particle-based Approach to Whole-cell Modelling. Int. E.coli. Alliance (IECA) Conference on Systems Biology, Program and Abstracts, Banff, Alberta, Canada, June 18-22: 13.

Lopez-Campistrous A, Semchuk P, Burke L, Palmer-Stone T, Garen G, Brokx S, Broderick G, Bottorff D, Locke T, Weiner J, 2004. Localisation and Annotation of the Escherichia coli K-12 Proteome in the Presence and Absence of Amino Acids. Int. E.coli. Alliance (IECA) Conference on Systems Biology, Program and Abstracts, Banff, Alberta, Canada, June 18-22.

Broderick G, Ru'aini M, Winters P, Chan E, Ellison MJ, 2004. Towards a Life-like Virtual Cell Using Discrete Automata. Departmental Seminars in Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta, Canada, December 2.

Ellison MJ, Broderick, G, Ru'aini M, Bottorff D, Weiner J, 2003. A massively Parallel Arithmetic Approach to Whole-cell Modelling in 4-D. First Int. E.coli. Alliance (IECA) Conference on Systems Biology, Program and Abstracts, Tsuroka, Japan, June 23-25: 24.

Tessier P, Broderick G, 2000. Example Applications of Multivariate Statistical Analysis in the Pulp and Paper Industry. Proc. PAPTAC Conf., Montreal, January 31-Feb 4.

Graff S, Broderick G, Tessier P, Leger R, 2000. Predictive Models of Effluent Treatment at Fraser Paper in Edmundston. Proc. Tappi 2000 Environmental Conf., Denver, CO, May 7-10.

Pudlas M, Broderick G, Tessier P, 2000. Assessing Competitive Position Using Multivariate Statistical Analysis of Pulp Quality. Proc. PACWEST Conference 2000, Pulp and Paper Technical Assoc. of Canada, Jasper, A.B., June 1-4.

Tessier P, Broderick G, Desrochers C, Bussiere S, 1997. Motor Load and Freeness Control of Chemimechanical Pulp Refining: Industrial Results. European Control Conference, Brussels, Belgium, July 1-4.

Broderick G, Tessier P, 1996. On-line Fibre Quality Sensors: What They Should Measure and Why. Pulp Expert User Seminar, Pulp Expert Oy, Montreal, September 30.

Broderick G, 1996. PLS and Latent Vector Modelling: A Decision Support Tool. Technical Session, CPPA Process Control Committee, Vancouver, September 23.

Broderick G, Paris J, Valade JL, 1993. The Impact of Processing Conditions on Spent Sulphite Liquor Toxicity. Proc.43rd Canadian Chemical Engineering Conf., Ottawa, Ont., Oct. 3-6: 206.

Broderick G, Valade JL, Paris J, 1991. Identifying Dominant Process Factors in High Yield Sulphite Pulping Using a Plackett-Burman Design. Proc.41st Canadian Chemical Engineering Conf., Vancouver, Oct. 6-9: 19-5.

Proceedings

Benz-Zvi A, Lee JM, Broderick G, 2009, An MPC-based Approach to Robust Control of a Hypothalamic-Pituitary-Adrenal Axis Model. 6th IFAC Symposium on Robust Control Design, Haifa, Israel, June 16-18: paper TuM1.1.

Tessier P, Broderick G, Plouffe P, 2000. Competitive Analysis of North-American Newsprint Producers Using Composite Statistical Indicators of Product and Process Performance. Proc. Control Systems 2000, Pulp and Paper Technical Assoc. of Canada, Victoria, BC , May 1-4: 263-266.

Broderick G, Tessier P, Desrochers C, Bussiere S, 1998. On-line Prediction of Newsprint Furnish Quality Using Multivariate Statistical Models. Proc. Control Systems 98, Finnish Society of Automation, Porvoo, Finland, Sept. 1-3: 135-142.

Tessier P, Broderick G, Desrochers C, Bussiere S, 1998. Refiner Pulp Quality Control Using PLS Transforms. Proc. Control Systems 98, Finnish Society of Automation, Porvoo, Finland, Sept. 1-3: 160-167.

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Broderick G, Cacchione E, Heroux Y, 1996. The Importance of Distribution Statistics in the Characterisation of Chip Quality. Proc. Tappi Pulping Conf., Nashville, TN, Oct. 27-31, Book 2: 535-549.

Broderick G, Paris J, Valade JL, 1994. Fibre Development in Chemimechanical Pulp Refining. Proc. Tappi Pulping Conf., San Diego, CA, Nov. 6-10: 435-443.

Broderick G, Paris J, Valade JL, 1994. Monitoring Composite Pulp Quality. Proc. 80th Annual Meeting CPPA Technical Section, Montreal, Feb. 1-4: B35-B40.

Lanouette R, Broderick G, Valade JL, 1994. L'Optimisation du raffinage par la modélisation statistique. Proc. Conférence Technologique Estivale, Pointe-au-Pic, June 1-3 : 1-9.

Broderick G, Valade JL, Paris J, 1992. High Yield Sulphite Pulping Based on a Plackett-Burman Design. The 78th Annual Meeting CPPA Technical Section, Montreal, Jan. 28-31: A141-A146.

Patents.
Broderick G, Ru'aini M, Ellison MJ, 2004. System and Method for Simulating Biological Cell Membrane Processes. Patent Cooperation Treaty PCT/CA2005/000795 (May 25, 2005), U.S. provisional patent appl. #60/575,089 (May 28, 2004).

Ellison MJ, Broderick G, Ru'aini M, Bottorff D, Wishart D, 2004. System and Method for Simulating Living Cell Processes. Patent Cooperation Treaty PCT/CA2004/000369 (May 5, 2004), U.S. provisional patent appl. #60/453,257 (March 10, 2003).

Broderick G, Lanouette R, Valade JL, 1995. Optimal Energy Refining Method for the Mechanical Treatment of Wood Fibres. Canadian patent 2,150,647 (November 30, 95), U.S. patent 5,540,392 (July 30, 1996).

TEACHING
Undergraduate Teaching Activities.
DMED 514 – Cardiovascular Winter 2010
Small group facilitator
Overall effectiveness rating 9.8/10.0

MED524 Neurosciences and Organs of Special Senses (A)
Small group facilitator
Overall effectiveness rating 9.4/10.0

DMED 512 - Infection, Immunity and Inflammation Fall 2009
Small group facilitator
Overall effectiveness rating 9.4/10.0

MED522 Reproductive Medicine and Urology
Small group facilitator
Overall effectiveness rating 10.0/10.0

MED526/DDS520 Patient-centred Care
Small group facilitator
Overall effectiveness rating TBD

MED524/DDS507 Neurosciences and Organs of Special Senses Winter 2009
Discovery learning (DL) small group facilitator
Part A. Overall effectiveness rating 10.0/10.0
Part B. Overall effectiveness rating TBD

MED515 Community Health
Small group facilitator
Overall effectiveness rating 9.8/10.0

MED526/DDS520 Patient-centred Care II
Small group facilitator
Section III. Session on Fibromyalgia and Allied Conditions
Section IV. Session on Mental Health Site Visits

Section IV. Session on Alzheimer's
Overall effectiveness rating 8.0/10.0

MED516 /DDS510 Patient-centred Care I Fall 2008
Small group facilitator; Session on Voluntariness

MED526 /DDS520 Patient-centred Care I
Small group facilitator; Session on diabetes

MED521 /DDS506 – Gastroenterology and Nutrition
Discovery learning (DL) small group facilitator
Overall effectiveness rating 9.8/10.0

Substitute Teaching as Discovery Learning (DL) small group facilitator in:
DMED 512 - Infection, Immunity and Inflammation
DMED 513 – Endocrinology and Metabolism

DMED 514 – Cardiovascular, Pulmonary and Renal Systems Winter 2008
Discovery learning (DL) small group facilitator
Renal Block; Overall effectiveness rating 9.4/10.0
Pulmonary Block; Overall effectiveness rating 9.1/10.0
Cardiology Block; Overall effectiveness rating 9.4/10.0.

DMED 512 - Infection, Immunity and Inflammation Fall 2007
Discovery learning (DL) small group facilitator
Overall effectiveness rating 9.2/10.0

DMED 514 - Cardiovascular, Pulmonary and Renal Systems. Winter 2007
Discovery learning (DL) small group facilitator;
Renal Block; Overall effectiveness rating 9.4/10.0
Pulmonary Block; Overall effectiveness rating 10.0/10.0.

Undergraduate Research Supervision / Co-supervision
Mr. Scott deGraff Summer 2010
Immune Network Dynamics in Gulf War Illness

Mr. Landon Berger Summer 2009
Immune Biomarkers of Multiple Sclerosis in Cerebral Spinal Fluid

Ms. Andrea Kreitz Summer 2009
Emergent Patterns of Cytokine Expression in Chronic Fatigue Syndrome and Gulf War Illness

Ms. Christina Yang Summer 2009
A Computational Study of Neuronal Migration in the Developing Neocortex
Recipient of the Henry Anton Deutsch Medical Summer Research Award

Mr. Michael Gallagher 2008- 2009
A Computational Study of Neuronal Migration in the Developing Neocortex

Ms. Ann Aspler and Ms Carly Bolshin Summer 2007
Evidence of Altered Neuroendocrine- immune Function in a Population-based Study of Chronic Fatigue Syndrome.

Mr. Bernhard Handle (senior year design project) 1995-1996
Hydrometallurgical electro-refining of high-purity tellurium
Supervisor: Dr. P. Paschen, Montan-University, Leoben, Austria

Graduate Teaching.
MTH 6301 Statistical Design and Analysis of Experiments Winter 1995
Dept. Appl. Mathematics and Industrial Engineering, École Polytechnique de Montréal
Adjunct Professor, developed and taught graduate course linking linear regression theory to the construction and analysis of multivariable experimental studies.

Graduate Supervision/ Co-supervision
Paule Marceau (M.Sc.) - Industry Co-supervisor 1997-2001
Modeling the impact of particle size distribution of mechanical properties of wood composites
Supervisor : Dr. A. Cloutier (Université Laval)

Brendan Cote (M.Sc.) - Industry Co-supervisor 1997-2000
Applicability of advanced computational networks to the modeling of complex geometry
Supervisor: Dr. D. Thérien (McGill University)

Jean Sébastien Bolduc - Industry Co-supervisor 1996-1998
Cellular-automata based nonlinear adaptive controllers
Supervisor: Dr. D. Therein (McGill University)

Bodhana Ratitch - Industry Co-supervisor 1996- 1998
Continuous function identification with fuzzy cellular automata
Supervisor: Dr. D. Thérien (McGill University)

Trevor Fenton - Industry Co-supervisor 1996- 1997
Finite element modeling of porous networks of composite materials
Supervisor: Dr. H. Budman (University of Waterloo)

Timothy Knapp - Industry Co-supervisor 1996- 1997
Adaptive geometry neural network based control of chemical processes
Supervisor: Dr. H. Budman (University of Waterloo)

Postgraduate Teaching/ Supervision.
Supervision of post-doctoral research **2007 – present**
Mr. J Fuite (PhD 2007)
A Network Theoretical Study of Neuro-immune Deficiency in Chronic Fatigue and Gulf war Illness.

Supervision of research associate **2006 –2007**
Mr. Eric Carpenter
Bi-stability in repair from injury and rejection of kidney allografts

OTHER PROFESSIONAL AND SCHOLARLY ACTIVITIES
International Committees
Invited member July 2010
International Panel for Canadian Consensus Document on ME/CFS

Invited member Jan. 2010
US Veteran's Administration Planning Committee for Gulf War Illness Genome-wide Association Study (CSP #585)

Associate Editor, Mar. 2010
BMC Systems Biology, BioMed Central, London, UK

Administrative and Research Committees

Member Aug. 2007 – present
Department of Medicine Research Committee

Member July 2006 - present
Division of Pulmonary Medicine

Head Computational Biology July 2006 - present
Management Committee - Alberta Transplant Applied Genomics Centre

Voting member Sept. 2006 - present
Scientific Management Executive Committee - Transplant Transcriptome Project
Genome Alberta/ Genome Canada

Member Mar. 2007 - present
Faculty Committee for Review of the Institute for Biomolecular Design

Member Oct. 2007 - present
Faculty Committee for University Wireless Services

Student academic committees.

Member Sept. 2006 - present
Ph.D. Committee – Mr. Zhipeng Cai
Dept. of Computer Science, University of Alberta

Member Oct. 2006 - present
Ph.D. Committee – Mr. Anmmd Kamruzzaman
School of Public Health, University of Alberta

Organising committees Nov. 2006 – June 2007
Organising Committee member
Session Chair - Numerical Techniques for Creating Biological Insights
"Omic" Technologies to Phenotype Disease: A Satellite Symposium of the 9th Banff Conference on Allograft Pathology, Edmonton, AB. Jun

Appendix H: Mary Ann Fletcher Curriculum Vitae

UNIVERSITY OF MIAMI
Curriculum Vitae

Date: January 28, 2010

I. PERSONAL

1. Name: Mary Ann Fletcher
2. Home Phone: 305-596-5535
3. Office Phone: 305243-6288
4. Home Address: 10700 SW 90th Ave, Miami, FL 33176
5. Current Academic Rank: Professor, tenured
6. Primary Department: Medicine
7. Secondary Appointments: Microbiology/Immunology; Psychology; Pediatrics, member of the Graduate Faculty
8. Citizenship: USA

II. HIGHER EDUCATION

1. Texas Technological College, B.S. (honors), 1959
2. University of Texas, M.A., 1961
3. Baylor University, Ph.D., 1966
4. Northwestern University, postdoctoral fellowship, 1966-68

III. CERTIFICATIONS AND LICENSURES

1. Diplomat American Board of Bioanalysis - High Complexity Laboratory Director, Clinical & Technical Consultant
2. State of Florida licensed and CLIA certified as Clinical Laboratory Director

IV. EXPERIEINCE

1. 1981 - Present: Tenured Professor of Medicine, University of Miami Miller School of Medicine, Miami, FL
2. 1982 - Present: Professor of Microbiology/Immunology, UM Miami School of Medicine, Miami, FL
3. 1989 - Present: Professor of Psychology, UM, Coral Gables, FL
4. 1982 - Present: Director, E.M. Papper Clinical Immunology Laboratory, UM School of Medicine, Miami, FL
5. 1978 - Present: Member of the Graduate Faculty, UM, Coral Gables, FL
6. 1978 -1981: Associate Professor of Microbiology, UM School of Medicine, Miami, FL
7. 1977 - 1981: Tenured Associate Professor of Medicine, UM School of Medicine, Miami, FL
8. 1972 – 1976 : Assistant Professor of Medicine, UM School of Medicine, Miami, FL
9. 1970 - 1972: Adjunct Assistant Professor of Biology, Illinois Institute of Technology, Chicago, IL
10. 1969 -1972: Assistant Director, Division of Hematology, Michael Reese Hospital and Medical Center, Chicago, IL
11. 1969 -1972: Assistant Attending Physician, Special Staff, Michael Reese Hospital and Medical Center, Chicago, IL..

12. 1967 -1969: Instructor and Asst Professor, Dept. Microbiology, Northwestern University Medical School, Chicago, IL
13. 1966 - 1969: Postdoctoral fellow, Northwestern University, Evanston Hospital, Evanston, IL
14. 1963 - 1966: Research Associate, Graduate Research Institute of Baylor University, Dallas, TX
15. 1962 - 1963: Clinical Bacteriologist, Spohn Hospital & Driscoll Found. Hospital, Corpus Christi, TX
16. 1959 - 1961: Research Assistant, Dept Microbiology, Univ. of Texas, Southwestern Medical School, Dallas, TX.

V. PUBLICATIONS (BOOKS AND MONOGRAPHS)

1. Springer, G.F., Fletcher, M.A, and Pavlovskis, O. Homogeneous Erythrocyte Glycoproteins with Blood Group -, Virus -, and Endotoxin Receptor Activities. In *Protides of the Biological Fluids* 15:109-122, 1967, H. Peeters, ed., Elsevier Pub. Co., Amsterdam.
2. Springer, G.F., Fletcher, M.A: Cell Surface Receptors: Structural Aspects and Importance in Immunopathology In *Organ Transplantation*, pp47-62, Hymer and Ricken, eds., Schattauer, Stuttgart, 1969.
3. Levey, G.S., Fletcher, M.A. and Klein, I. Glucagon and Adenylate Cyclase: Binding Studies and Requirements for Activation. In *Advances In Cyclic Nucleotide Research,* Vol. 5, edited by G.I. Drummon, P. Greengard, and G. Robinson, Raven Press, New York, 1975.
4. Levey, G., Fletcher, M.A and S. Ramachandran: Methods to Characterize the Cardiac Glucagon Receptor. In *Methods in Receptor Research*, edited by M. Blecker, pp. 143-147, Marcel Dekker, Inc., New York, 1976.
5. Fletcher, M.A, Lo, T.M. and Graves, W.R.: Glycoproteins from the Bovine Erythrocyte Membrane. Glycoconjugate Research Vol. II. *Proceedings of the Fourth International Symposium On Glycoconjugates.* R. Jeanloz., Academic Press, Inc. N.Y. pg. 1047-1050, 1978.
6. Fletcher, M.A., Lo, T.M. and Caldwell, K.E.: Interaction of Limulin with Membrane Glycoproteins, *Biomedical Applications of the Horseshoe Crab (Limulidae)* E. Cohen, ed., Alan Liss, Inc. N.Y. pg. 655-664,1979.
7. Claflin, A.J., McKinney, E.C and Fletcher, M.A.: Immunologic Studies of Prostate Adenocarcinoma In Animal Models. *Model System For Prostate Cancer*, G. Murphy, ed., Alan Liss, Inc. N.Y., 365-376, 1980.
8. Saez, L., Latif, A., Caldwell, K. and Fletcher, M.A.: Heterophile Antigen Common to Human Tissues and Bovine Erythrocytes. in *HLA Antigens In Health, Aging and Malignancy*, (Cohen, E. and Singa, D.P., ed.) Alan R. Liss, Inc., New York, pp. 221-225, 1983.
9. Caldwell, K.E. and Fletcher, M.A A Paul-Bunnell Antibody Reactive Glycoprotein From Canine Erythrocyte Membranes. In *Glycoconjugates*, Davidson, E.A., Williams, J.C. and DiFerrante, N.M., eds., Prager, N.Y. p590-590, 1986.
10. Fletcher, M.A., Caldwell, K.E. and Klimas, N.G. The Use of Glycoprotein-Latex Conjugates in a Rapid Slide Test for Paul-Bunnell (P-B) Antibodies in Unabsorbed Sera. *Clinical Immunology* Pruzanski, W, Seligmann, M., eds, Elsevier Science Publ., Amsterdam, pg 247-250, 1987.
11. LaPerriere, A., Schneiderman, N., Antoni, A. and Fletcher, M.A. Aerobic Exercise Training and Psychoneuroimmunology in AIDS Research. in *Psychosocial Aspects of AIDS*. edited by L. Temoshok and A. Baum. Lawrence Erbaum and Associates, 1990.
12. Klimas, N.G., Baron, G.C. and Fletcher, M.A. The Immunology of HIV-1 Infection. in *Stress, Coping and Disease* edited by Schneiderman, N., McCabe, P., Fields, T. and Skyler, J. Lawrence Erlbaum and Associates, Hillsdale, N.J. p193-209, 1991.
13. Fletcher, M.A., Klimas, N.G., Morgan, R. and Gjerset, G. Lymphocyte Proliferation Assays. in *Manual of Clinical Laboratory Immunology*, 4th edition, Rose, N. and Fahey, J. eds., Amer. Soc. Microbiology. pg. 213-219, 1992.
14. LaPerriere, A., Antoni, M., Klimas, N.G., Schneiderman, N. and Fletcher, M.A. Psychoimmunology and Stress Management in HIV-1 Infection. in *Update in Psychoneuroimmunology*, Gorman, J.M. and Kertzner, R.M., eds. Progress in Psychiatry, #35, Spiegel, D. series ed., American Psychiatric Press, Washington, D.C., p. 81-112, 1991.
15. LaPerriere, A., Antoni, M., Fletcher, M.A. and Schneiderman, N. Exercise and Health Maintenance in AIDS. In *Clinical Assessment and Treatment in HIV: Rehabilitation of a Chronic Illness.* Galantino, F., ed., Slack, Inc., Thorofare, NJ. pg.65 - 76, 1992.
16. Klimas, N.G., Morgan, R., Salvato, F., Flavia, Van Reil, Millon, C. and Fletcher, M.A. Chronic Fatigue Syndrome and Psychoneuroimmunology. In *Stress and Disease Progression: Perspectives in Behavioral*

Medicine. Schneiderman, N., McCabe, P. and Baum, A., eds. Lawrence Erlbaum, Assoc., Hillsdale, NJ, P121-137, 1992.
17. Nash, M.S. and Fletcher, M.A., The Physiologic Perspective: Immune System, In. *Aging with Spinal Cord Injury.* Whiteneck, G.G., ed. Demos Publications, New York, pg. 159-181, 1992.
18. Antoni, M., Schneiderman, N., LaPerriere, A., Bourguinon, L. and Fletcher, M.A.. Psychoneuroimmunology and stress responses in HIV-1 seropositive and at-risk gay men. In *Stress and Disease Progression: Perspectives in Behavioral Medicine*. Schneiderman, N., McCabe, P. and Baum, A., eds. Lawrence Erlbaum, Assoc., Hillsdale, NJ, 139-163, 1992.
19. Antoni, M., Schneiderman, N., LaPerriere, A., O'Sullivan, M. and Fletcher, M.A.. Mothers with AIDS. in Ahmad, P. (ed). *Living and Dying with AIDS*. Phenum, N.Y. Pg. 45-86, 19
20. Klimas, N.G., Morgan, R., vanRiel, F.. and Fletcher, M.A., Clinical Observations Regarding Use of an Anti-Depressant, Fluoxetine. in Chronic Fatigue Syndrome, In *Chronic Fatigue Syndrome*, P. Goodnik and N.G. Klimas, eds., American Psychiatric Press, Washington, D.C., p95-108, 1993.
21. Patarca, R., Klimas, N.G., and Fletcher, M.A. Immunological Correlates of Chronic Fatigue Syndrome. in Chronic Fatigue Syndrome, In *Chronic Fatigue Syndrome*, P. Goodnik and N.G. Klimas, eds., American Psychiatric Press, Washington, D.C., p1-22, 1993.
22. Fletcher, M.A., Morgan, R. and Klimas, N.G. Immunologic Consequences of Treatment for Drug Abuse. In Friedman, H. et al., eds. *Drugs of Abuse, Immunity and AIDS*, Plenum Press, New York, p241-246, 1993.
23. Schneiderman, N, Antoni, M, Fletcher, MA, Tronson, G, Klimas, N, Kumar, M and LaPerriere, A. Endocrine responses, immunity and HIV spectrum disease, In Friedman, et al., eds, *Drugs of Abuse, Immunity and AIDS*. Plenum Press, New York, 1993.
24. Klimas, N.G., Fletcher, M.A., Walling, J., Garcia-Morales, R., Patarca, R., Moody, D. and Ocarma, T. Ex Vivo Expansion, Activation and re-infusion in to Donor with rIL-2 - a Phase 1 Study. in *Retroviruses of Human AIDS and Related Diseases*, Girard, R, M. and Valette, L., eds, in *8*th Colloque des Cent Gardes., pg. 285-290, 1992.
25. Antoni, M, Esterling, B, Lutgendorf, S, Fletcher, MA, and Schneiderman, N. Psychosocial Stressors, herpes virus reactivation and HIV infection. In Stein, M and Baum, A, eds. *AIDS and Oncology: Perspectives in Behavioral Medicine.* Erlbaum, Hillsdale, NJ, 1995.
26. Schneiderman, N., Antoni, M., Ironson, G., Klimas, N.G., LaPerriere, A., Kumar, M., Esterling, B. and Fletcher, M.A.. HIV-1, Immunity and Behavior. in *Handbook of Human Stress and Immunity*. ed by Glaser, R. and Kiecolt-Glaser. Academic Press, Inc. New York, 1995.
27. Goodkin, K., Blaney, N., Tuttle, R., Lehman, J. Feaster, D., Burkhalter, J., Leeds, B., Mahmood, R., Baum M., Kumar, M. and Fletcher, M.A. The psychoneuroimmunological impact of bereavement and a support group in HIV-1 infection. In Goodkin, K., ed. *Psychoneuroimmunology: Stress, Mental Disorders and Health.* American Psychiatric Press, Inc., Washington, D.C. , 1995.
28. Ironson, G., Antoni, M., Schneiderman, N., LaPerriere, A., Klimas, N. and Fletcher, M.A. Stress Management interventions and psychosocial predictors of progression in HIV-1 infection. in K. Goodkin, ed. *Psychoneuroimmunology, Stress, Mental Disorders and Health.* American Psychiatric Press, Washington, D.C., 1995.
29. Lutgendorf, S., Antoni, M., Schneiderman, N., Ironson, G. and Fletcher, M.A. Psychosocial interventions and quality of life changes across the HIV spectrum. in Baum, A. and Dimsdale, J., eds. *Perspectives in Behavioral Medicine*. Erlbaum, Hillsdale, N.J. 205-239, 1995.
30. Schneiderman, N, Antoni, M, Ironson, G, Lutgendorf, S, Hurwitz, B, Klimas, N, LaPerriere, A and Fletcher, MA. Psychoneuroimmunology und HIV/AIDS. In Schedolwski, M and Tewes, U, eds. *Psychoneuroimmunology*, Spektrum Akademischer Verlag, Germany, 577-633, 1996.
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32. Fletcher, M.A., Urban, R., Asthana, D., Walling, J., Friedlander, A. And J.B. Page. Lymphocyte proliferation in *Manual of Clinical Laboratory Immunology*, Rose, N., deMacario, E., Folds, J., Lane, H.C. and Nakamura, R., eds. ASM Press, Washington, D.C., p 313-319, 1997.
33. Patarca, R., Fletcher, M.A. and Podack, E. Cytolytic cell functions. in *Manual of Clinical Laboratory Immunology*, Rose, N., deMacario, E., Folds, J., Lane, H.C. and Nakamura, R., eds. ASM Press, Washington, D.C., p 296-303, 1997.
34. Patarca, R., Maher, K., Goodkin, K. and Fletcher, M.A. Cryopreservation of peripheral blood mononuclear cells in *Manual of Clinical Laboratory Immunology*, Rose, N., deMacario, E., Folds, J., Lane, H.C. and Nakamura, R., eds. ASM Press, Washington, D.C., p 281-286, 1997.
35. Fletcher, M.A., Ironson, G., Goodkin, K., Antoni, M., Schneiderman, N. and Klimas, M.A. Stress and

immune function in HIV-1 disease. In Workman, E. and Hubbard, J., eds. *Stress Medicine.* CRC Press, Boca Raton, FL, p229-242, 1998.

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210. Maher K, Klimas N, Dickinson G, Triplett J, Maggio C, Cohen V, Valenzuela R, and Fletcher MA. The Effect of Highly Active Anti-Retroviral Therapy on Viral Load and the Immune System in Human Immunodeficiency Virus (HIV) Infection. NY State Wadsworth Conference on HIV Laboratory Testing. Albany, NY, 1997
211. La Perriere, A, Goldstein, A., Klimas, N., Ironson, G., Majors, P, Maik, G., Talluto, C., Fletcher, M.A. and Schneiderman, N., Non-compliant exercise decreases CD4+ cells in early symptomatic HIV infection. Presented to the Society of Behavioral Medicine, San Francisco, CA, 1997.
212. Fletcher, MA Markers of immune progression in HIV. Presented to the Academy for Behavioral Medicine Research. Cape Cod, 1998.
213. Ortiz-Butcher, C, Pennell, JP, Walling, J, Zjacic, B and Fletcher, MA Analysis of hemodialysis by RT/PCR for HIV after accidental splash of a dialysis provider. Presented to the American Society of Nephrology, November 2-5, 1997.
214. Dixon, D., Antoni, M., Kilbourne, K., Wagner, S., Schneiderman, N. and Fletcher, MA. Social support buffers PTSD symptoms and HHV-6 antibody titers in HIV+ gay men following hurricane Andrew. Neuroimmunomodulation, 5: 15, 1998.
215. Maher K, Cruess D, Antoni M, Schneiderman N, Klimas K, and Fletcher MA. Associations Between Viral Load, Natural Killer Cell (CD56+CD3-) Number, and State Anxiety among HIV Seropositive Men. Research Perspectives in PsychoNeuroImmunology, Galveston, TX 1999.
216. Maher K and Fletcher MA Flow Cytometric Analysis of Natural Killer Cell Perforin Content Correlates with Lytic Potential Clinical Applications of Cytometry, Palm Springs, CA Cytometry, 38:341, 1999
217. Dixon, D., Antoni, M, Wagner, S., Kilbourn, K, Schneiderman, N, Klimas, N, Fletcher, MA Acute and sustained effects of anxiety on immune status and social support in HIV+ gay men following Hurricane Andrew, Neuroimmunomodulation. 6:214, 1999.
218. Dixon, D. Crues, S., Kilbourne, Klimas, N, Fletcher, MA., Ironson, G, Baum, A, Schneiderman, N, and Antoni, M. Social support mediates the relationship between loneliness and human herpesvirus-6 (HHV-6) antibody titers. Presented at the annual meeting of the PsychoNeuroImmunology Research Society, Cape Fear, NC 2000.
219. Fletcher, M.A., Patarca, R., Maher, K., Antoni, M, Klimas, N. Symposium: Multidisciplinary studies of chronic fatigue syndrome. Int. J. Beh. Med. 7: suppl 1:98-100, 2000.
220. Fletcher, M.A., Ironson, G., Solomon, G., Balbin, E., Klimas, N. and Schneiderman, N. Can non-specific cellular immunity protect HIV-infected persons with very low CD4 counts? Presented at Conference on Integrating Psychology and Medicine, Waheki Island, Auckland, NZ, 10-12th Nov., 2000.
221. Weiss, D, Pereira, D, Antoni, M, Fletcher, MA, Siegel, S, Klimas, N. A group-based intervention enhances coping and energy level and decreases depression in chronic fatigue syndrome. 7th International Congress of Behavioral Medicine, Helsinki. Int. J. Behavioral Med 9:292-293, 2002.
222. Ironson, G, Solomon, G, Balbin, E, O'Cleirigh, C, Schneiderman, N and Fletcher, MA. Psychosocial factors related to sustained health in HIV. . 7th International Congress of Behavioral Medicine, Helsinki. Int. J. Behavioral Med 9:126, 2002.
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224. Siegel S, Segesta MC, Antoni m, Maher K, Fletcher MA , Weiss D, Klimas N. A Group-Based Cognitive Behavioral Stress Management Intervention Improves Psychosocial and Medical Outcomes in Chronic Fatigue Syndrome. American Psychosomatic Society, 2004.
225. Balbin E, Ironson G, Ditz K, Fletcher MA. Gay disclosure to family, friends and coworkers: relation to changes in both CD 4 and viral load in HIV/AIDS. American Psychosomatic Society, 2004.

226. Shor-Posner G, Hernandez-Reif M, Baez J, Soto S, Miguez M-J, Perez-Then E, Fletcher MA, Diaz R, Zhang G. Massage therapy intervention to enhance well-being in HIV+ Dominican children: preliminary results XV AIDS MEETING in Barcelona, Spain, 2004.
227. Klimas N, Fletcher MA, Maher K.. Elevations of HHV-6 serology are associated with low NK cell Function. International Conference on HHV6 Infection, Barcelona Spain May1-3, 2006.
228. Klimas NG, Rosenthal M, Fletcher MA.. Immune effects of an acute exercise challenge in Gulf War Illness. Assoc Military Surgeons US. San Antonio, TX, 2006.
229. Ironson G, Stuezle R, Fletcher MA, View of God is Associated with Disease Progression in HIV. Society of Behavioral Medicine March 22- 25, 2006 San Francisco. Paper Abstract published in Annals of Behavioral Medicine, 31 (Supplement), 2006; S074.
230. Traeger L. Penedo F, Rasheed M, Zhou E, Fletcher MA, Scheiderman N, Antoni M. Cortisol mediates the relationship between stress management skills and prostate-specific antigen (PSA) level among men treated for prostate cancer. American Psychosomatic Society, 2007.
231. Ironson G, Balbin E, Stieren E, Detz K, Fletcher MA, Schneiderman N, Kumar M. Perceived stress and norepinepherine predict the effectiveness of the response to protenase inhibitor medication in HIV. American Psychosomatic Society, 2007.
232. Fletcher MA, , X-R Zeng, M Rosenthal, X-Q Jin, G Godoy, Jr & NG Klimas. Immunological Comparison of GWI and CFS. 9th International Association of CFS/ME meeting, Ft. Lauderdale, Fl, 2007.
233. Sussex A, Fekete EE, Antoni M, Gonzales J, Penedo F, Fletcher M, Klimas N, MacPherson S, Horne R, Schneiderman N. Support From Health Care Providers, Medication Attributions, HAART Adherence And Viral Load In HIV+ Low-Income Minority Women. American Pschosomatic Society, Baltimore, Md., March, 2008.
234. Fletcher MA. Neuropeptide Y and dipeptidyl peptidase IV (CD26) in chronic fatigue syndrome. 1st Annual Meeting of Neuroimmune Mechanisms and Chronic Fatigue Syndrome. NIH June 20, 2008.
235. Fletcher MA. Progress in identification of biomarkers for CFS and GWI. The Academy for Behavioral Medicine Research. Lake Louise, Canada, June, 2008.
236. Fletcher MA. Dipeptidyl peptidase IV(DDPIV/CD26) and neuropeptide y (NPY): Biomarkers for chronic fatigue syndrome. International Conf on Fatigue Science. Okinawa, Japan, September, 2008.
237. Lopez C, Fekete E, Antoni M, Fletcher MA, Mendez A, Sussex A and Schneiderman N. Oxytocin is Associated with Better Immune Function in Low Income HIV+ Women with High Perceived Social Support. Society of Behavioral Medicine, 2009.
238. Fletcher MA., Ironson, G, Antoni, M, Hurwitz, Klimas N. Neuropeptide Y (NPY) correlates with symptom severity in chronic fatigue syndrome. 9th International IACFS/ME Research and Clinical Conference. Reno, NV. March 2009.
239. Fletcher MA, Klimas NG and Broderick G. Neuroimmune biomarkers in CFS. From infection to neurometabolism: a nexus for CFS, a NIH sponsored workshop. Banbury Center, Cold Springs Harbor Laboratory, Long Island, NY. September, 2009

IX. FUNDED RESEARCH (LAST FIVE YEARS)

Active

Immunologic Mechanisms, Biomarkers and Subsets in CFS
NIAID R01AI065723 (PI MA Fletcher) 12/1/06 – 11/30/11
Goal of this project is to determine the immunologic basis for CFS pathogenesis
Role: PI, 25% effort

The Use of Comprehensive Molecular Profiling with Network and Control in GWI
GW080152 DOD (PI N Klimas)
07/15/2009 - 06/14/2011
GWI patients will be studied using gene array technology and neuron-endocrine-immunologic profiling pre-post exercise challenge.
Role: co-PI, 20% effort

University of Miami Developmental Center for Aids Research (D-CFAR)
NIAID SB04 1P30AI073961 (PI S Pahwa) 2007 – 2010

Direct core immunology lab for DCFAR members, Serve on developmental grants committee.
Role: Core lab director, 2.5% effort

Completed
Neuropeptide Y and dipeptidyl-peptidase IV (CD26) in chronic fatigue syndrome
NIAAA R21AA016635 (PI MA Fletcher) 9/30/06-5/31/09
Goal of this project to determine the relationship of neuropeptide Y and dipeptidyl-peptidase IV to natural killer cell cytotoxicity in CFS.
Role: PI, 20% effort

Psychobiological Processes and Health in HIV.
NIMH R01 (PI G. Ironson) 7/01/03-5/31/09
This grant examines psychological and biological (CTL, NK, cortisol) predictors of disease progression in HIV/AIDS.
Role: CoI. 5% effort

Patterns of Gene Activation in Gulf War Illness and Chronic Fatigue Syndrome
VA Merit Review, (PI N Klimas). 11/04 -11/09
Male and Female GWI and CFS patients will be studied using gene array technology pre-post exercise challenge.
Role: Co-PI, 10% effort

Efficacy of an Emotional Exposure Intervention in HIV.
NCCAM R01 (PI G. Ironson) 7/01/03-6/30/08
This study investigates the efficacy of emotional exposure and depth processing though writing on well being in patients with HIV/AIDS.
Role: Co.I. 5% effort

HIV/HCV Co-infection: HAART and Pathophysiology
NIHLBI R01 (PI B Hurwitz) 7/31/04 to 8/31/07
This study looks at the interactions of HAART and co-infection with HCV on the pathophysiology of HIV/AIDS
Role: Co-I, 5% effort

Massage Benefits in HIV+ Children: Mechanisms of Action
NCCAM R01AT002689 (PI G. Shor-Posner) 01/01/05-03/31/07
The two-fold intent of the above proposal is to evaluate the impact of massage therapy on immune recovery, and to investigate a potential neuroimmune mechanism of massage action.
Role: Co.I. 10% effort,

Center for Multidisciplinary studies of CFS
NIAID UO1- AI- 459940 (PI N Klimas) 8/1/00 to 7/31/05
This was a study of the modification of the stress response through a program of cognitive behavioral stress management and its effect on immune function in patients with chronic fatigue syndrome.
Role: Project Leader and Core Leader

Center for Psycho-Oncology Research
NCI IMO1-RR16587 (PI M Antoni) 10/1/99 to 9/30/05
The center was devoted to the mind/body interactions in patients with cancer.
Role: Core Leader

X. PROFESSIONAL SOCIETIES

American Association of Immunologists; American Society for Microbiology; American Society for the Advancement of Science; Society for Complex Carbohydrates; Association of Women in Science; Society for Experimental Biology and Medicine; Society for Clinical Cytology; Association of Medical Laboratory Immunologists, Steering Committee, 1987; Clinical Immunology Society; PsychoNeuroImmunology Research

Society, Scientific Affairs Committee - 1993 1995; American Association of Bioanalysts, Association of Clinical Chemists

XI. HONORARY SOCIETIES

Phi Kappa Phi, Alpha Epsilon Delta, Alpha Lambda Delta, Sigma XI, Fellow - Academy for Behavioral Medicine Research

XII. CONSULTANTSHIPS

National Cancer Institute (NCI), Tumor Immunology Review Committee 1980 - 1982

NCI - Clinical Cancer Program Project Review Committee Site Visit Participant, 1978 - 1984

National Science Foundation (NSF), Postdoctoral Fellowship Review Committee, 1979 - 1980

NSF Ad Hoc Review, 1979 - 1986

National Institutes of Health (NIH), Immunotechnology Special Review Committee, 1986-87

National Institute of Mental Health (NIMH), Psychoneuroimmunology Training Grants, Site Visitor, 1987 and Special Review Committee, 2004.

National Institute of Drug Abuse (NIDA), Site Visitor, 1988

National Heart, Lung and Blood Institute (NHLBI), Site Visitor, Special Review Committee 1989, 1993, 1998.

National Institute of Allergy and Infectious Diseases (NIAID), Special Review Committee, In vitro methods for AIDS Clinical Trials, 1995

NIAID, Ad Hoc reviewer for AIDS study section, 1991;

NIAID, Special Review Committee for Pediatric AIDS, 1995

NIAID, HIV Vaccine Development Review Committee, 1996, 1997, 1999, 2002 - 2005

NIAID, Special Review Committee for CFAR proposals, 2002, 2003

NIAID, HIV Special Emphasis Panel, 2004

NIH, CFS/FMS/TMD Review Panel, 2007, 2010

NIAID, Special Review Committee, 2007, 2008, 2010

XIII. EDITORIAL BOARDS AND REVIEWING

Clinical Applications in Cytometry; Clinical and Diagnostic Immunology; Journal of Chronic Fatigue Syndrome; Clinical and Applied Immunology Reviews ; Section editor: ASM Manual of Medical Laboratory Immunology, 5th edition. Ad Hoc reviewer, FASEB, Natural Immunity, Annals Internal Medicine, Psychosomatic Medicine, Brain Behavior and Immunity, Journal Infectious Diseases

XIV. TEACHING

Specialization: Immunology, Medical Laboratory Immunology, Psychoneuroimmunology

Mentor: Pre-doctoral trainees:

Martin Rosenthal, 2006-2008
Zackary Barnes, 2008-2009
Natalie Hone, 2009

Mentor - Ph.D. candidates:

Karen Caldwell, Ph.D., M.D. 1982 - 1989
George Ann Baron, Ph.D. 1983 - 1987
Brian Esterling, Ph.D. 1989 - 1991

Mentor – Post-doctoral fellows:

Patricia Kozlovskis, Ph.D.1980-1981
Zuhair Latif, Ph.D.1980-1983
Nancy Klimas, M.D.1983-1984
Lisetti Said, M.D.1980-1983
Gerson Silveria, M.D.1984-1985
Olga Torres, M.D. 1985-1986
Fernando Salvato, M.D.1987-1989
Roberto Patarca, Ph.D. M.D. 1990-1994
Kevin Maher, Ph.D., 1993-1994
Hector Pons, Ph.D., 1994-1995
Maria Jose Miquez-Burbano, M.D. 1994-1996
Desh Asthana, Ph.D., 1994 - 1997
Denise Dixon, Ph.D., 1997 – 1999
Lina Garcia, M.D., 2007-2009
Maria Vera, 2008-2009

Thesis and Dissertation Committees:

Elaine Young 1976-1978
Stephen Obenauf 1979-1983
David Charish 1979-1982
Caroline Petty 1979-1982
Scott Buessow 1984-1984
Alicia Sinclair 1984-1985
Marijane Montogomery 1984-1985
Gordon Watson 1985-1989
Peter O'Hearn 1986-1989
Arthur Laperrier 1987-1988
H. Lane Bagget 1989-1990
Sharon August 1990-1991
Andrea Friedman 1990-1993
Kathleen Starr 1992-1995
Susan Lugtendorf 1993-1994
Teresa Woods 1996-1998
Deidre Pereira 1996-1998
Mark Zuckerman 1996-1998
Frank Penedo 1997- 1999
Saroch Motivala 1997- 1999
John Malonovitch 1997- 1999
Staci Wagner 1998 - 2001
Kristian Kilbourn 1999 - 2002
Tammy Enos 1998- 2001
Steven Burke, 1999-2002
Connor O'Cleirigh 2000 -2006

Adam Carrico 2004 – 2007
Orit Weitzman 2004
Blake Scalon 2005 – 2007
Corina Lopez 2009 -

XV. SCHOOL AND DEPARTMENTAL COMMITTEES AND OFFICES

1. Medical School Council, 1976-1978. 2003-09
2. Faculty Senate Council Rep. to Medical School Council, 1979-1982.
3. School of Medicine Rep. to Consultative Committee for the Presidential Search, 1979-1981.
4. Admissions Committee, Ph.D.- M.D. 1974-1977.
5. Department of Medicine Research and Space Committee, 1978-1979.
6. Graduate School Faculty Screening Committee, 1980-1982, Chairperson, 1983
7. School of Medicine Rep. to Consultative Committee for Provost Search, 1982.
8. Scientific Advisory Committee, 1983-1985 (Chairperson); 1993-1996; 2002-07.
9. Appointment, Promotion and Tenure Committee, 1981-1984, 2007-10.
10. Institutional Self-Study, Faculty Review Subcommittee, Chairperson, 1986-1987.
11. Clinical Research Center - Protocol Review Committee, 1990-1992.
12. Center for AIDS Research - Steering Committee, 1989-1994.
13. Clinical Research Center, Executive Committee, 2008 -2009.
14. Scientific Review Committee for DCFAR Developmental Grant Applications. 2007 – 2009.

XVI. UNIVERSITY COMMITTEES & OFFICES

1. Faculty Rep. to Presidential Search and Selection Committee, 1979-1981.
2. Vice-Chairperson, Faculty Senate, 1979-1981.
3. Faculty Senate, 1979-82; 2000-03, 2003-12.
4. Faculty Senate Council Representative from School of Medicine, 1979-1982.
5. Academic Planning Committee, 1976-1978.
6. Academic Personnel Board, 1979-1981, 1992-1994.
7. Faculty Senate Committee on Committees, 1979-1981.
8. Women's Commission, President, 1984-1986.
9. President's Ad Hoc Committee on Research and Development - Chairperson of Subcommittee on Academic Affairs, 1981-1982.
10. Intercollegiate Athletics Governing Board, 1981-1982.
11. Research Council, 1982-1985.
12. Search Committee for Vice-President for Research and Dean of the Graduate School, 1984-1985
13. Consultative Committee for V.P. for Research & Dean of Grad. School, 1984-1985 (Chair).
14. University Self Study - Committee for Intercollegiate Athletics, 1985-1986.
15. Faculty Senate Committee for Rank, Salary and Conditions of Employment, 1987-1990 (Chair).
16. Faculty Senate Professional Conduct Committee, 1992 -1994 (Chair).
17. Faculty Senate Athletic Committee, 1993 - 1997, Chair, 1993-1994.
18. Faculty Senate Committee on Academic Services, 1997-1999.
19. Faculty Senate Committee on Women and Minorities, 2000-2004 (Chair).
20. Faculty Senate Committee on Institutional Priorities, 2000-2001.
21. Faculty Senate General Welfare Committee, 2004-2011.
22. Faculty Senate Ad Hoc Committee on Academic Freedom, 2008-2009.
23. Faculty Senate Ad Hoc Committee on Evaluation of Sub Deans, 2008-2009.

XVII. COMMUNITY ACTIVITIES

Health Crisis Network, Medical Advisory Committee, 1985
Women and AIDS Workshops, National Organization for Women, State and National Conferences, 1988, 1989, 1990, 1991, 1996, 1997.

Supporting Data

		YEAR 1 BUDGET July 1, 2009 - June 30, 2010
Payroll Expenses Including Fringes)	*$*	*38,428.17*
Contract Labor (UM subaward)	*$*	*81,541.19*
Material, Supplies, and Consumables	*$*	*26,105.03*
Travel Costs	*$*	*2,517.67*
Research Related Subject cost	*$*	*200.00*
Other expenses	*$*	*2,999.00*
Consultant (Ms. Sol)	*$*	*200.00*
Total direct Costs	***$***	***151,991.06***
Indirect cost	*$*	*37,997.76*
	$	***189,988.82***

All supporting figures and tables can be found in each pertaining journal publication.